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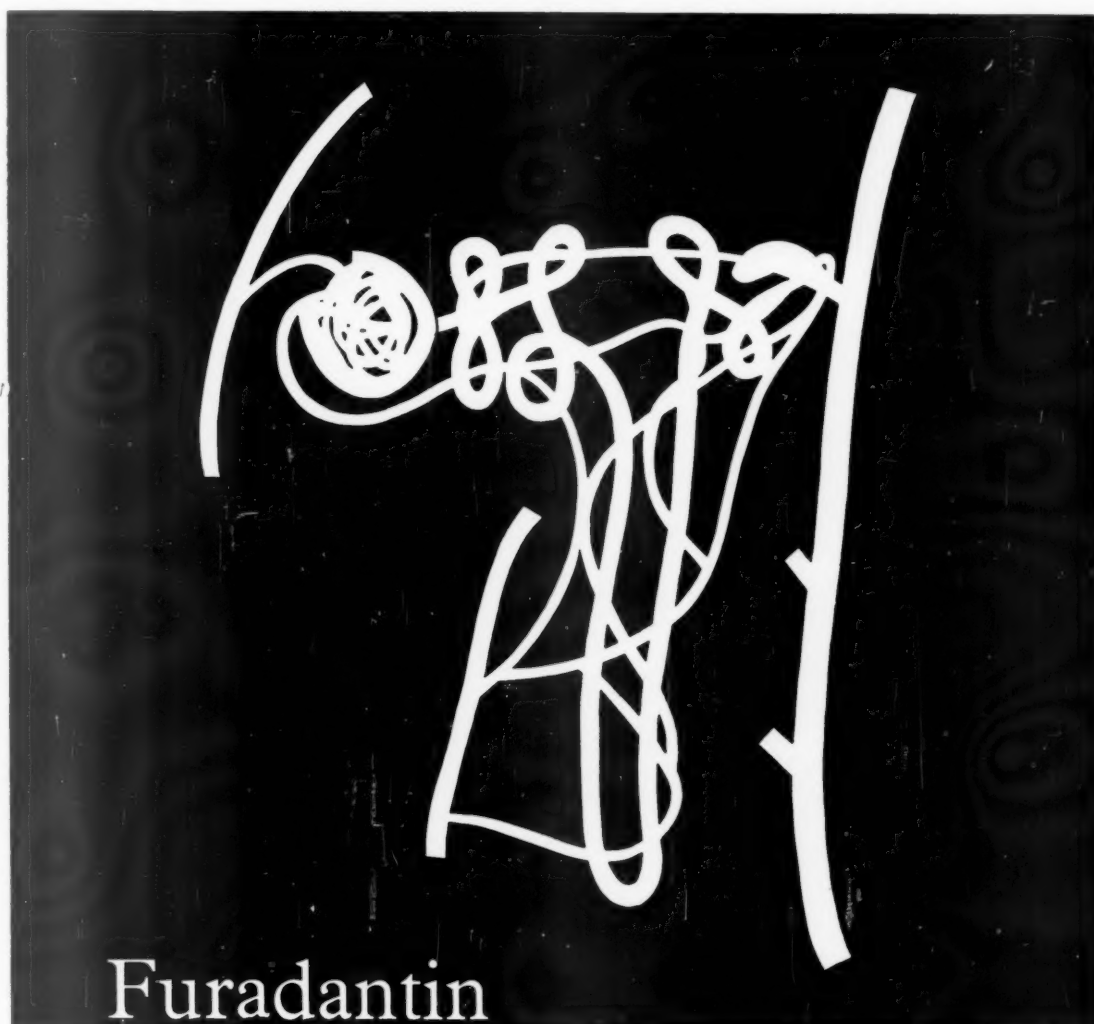
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# ON REAL AND APPARENT EXTERNAL BLEEDING IN THE NEWBORN

BY

W. S. CRAIG

*From the Department of Paediatrics and Child Health, the University of Leeds*

(RECEIVED FOR PUBLICATION APRIL 28, 1961)

Newborn infants are especially liable to haemorrhage. External bleeding is more frequent and associated with a more favourable prognosis than internal haemorrhage. Visible evidence of bleeding may appear in the superficial tissues, or in the form of haematemesis, melaena, haematuria or haemoptysis. In whatever situation, visible bleeding may be due to one or more causes. Thus blood in vomitus or expelled *per rectum* may be evidence of postnatal, foetal or maternal haemorrhage; and postnatal haemorrhage giving rise to haematemesis or melaena may originate in the gastro-intestinal tract or in the bucco-naso-pharynx. This paper presents a clinical study of the circumstances associated with visible bleeding seen in 345 newborn babies over the period January 1, 1949 to December 31, 1960.

## Material and Methods

Of the 345 infants, 253 were born in a maternity teaching hospital, 83 in their own homes and nine in nursing homes. There were 169 males and 176 females. The estimated gestation period of 102 babies was less than 38 weeks, and the birth weight of 78 was 5½ lb. or less. Delivery was normal in 263, instrumental in 51 and by caesarean section in 31 instances. The presentation was vertex in 302 and breech in 34 cases; the face or shoulders presented in nine cases.

All babies in the series were under the personal supervision of the writer. Those born in hospital were observed from the time of birth, and those born elsewhere from the time of admission to hospital on account of external bleeding. Clinical observations representing the agreed views of the senior nursing and medical staff were recorded daily or at shorter intervals. Bleeding in all the babies of the series was recognized in the course of naked eye examination, and clinical observations were confirmed in the case of melaena and haematemesis by use of the benzidine test and in the case of haematuria by use of the guaiac test. The presence

of large numbers of red blood cells on microscopical examination of bright red expectorated material was accepted as confirmation of haemoptysis.

The extent to which use was made of laboratory investigations was determined by the clinical characteristics of the bleeding and by the laboratory tests available at the time. The haemoglobin percentage and red blood cell counts were determined in the majority of infants. A haemoglobin of 70% (11.3 g. per 100 ml.) or less on the ninth or tenth day of life was accepted as evidence of anaemia. Prothrombin time estimations, using Quick's one-stage method, were carried out on 133 babies, using venous blood. A prothrombin time 75% or more in excess of that of a control adult plasma was accepted as evidence of a coagulation defect. In differentiating foetal from maternal blood use was made of alkali denaturation tests in the study of 43 cases; in nine of these confirmation was obtained by phase contrast microscopy.

## Clinical Findings

**Anatomical Site of the Haemorrhage.** In Table 1 the various forms of bleeding are grouped according to their anatomical situation.

**Miscellaneous Group (7).** Haemorrhage in the

TABLE 1  
INCIDENCE OF DIFFERENT TYPES OF BLEEDING  
IN 345 INFANTS

Type of Bleeding	No. of Infants
Gastro-intestinal .. ..	155
Cutaneous and subcutaneous .. ..	96
Cord/umbilicus .. ..	26
Haematuria .. ..	23
Post-natal superficial trauma .. ..	18
Haemoptysis .. ..	16
Bucco-nasopharyngeal .. ..	13
Following circumcision .. ..	12
Superficial laceration at delivery .. ..	7
Miscellaneous .. ..	7
Lachrymal duct .. ..	5
Vaginal (severe) .. ..	2

Bleeding of more than one type occurred in 24 infants.

two babies with bleeding from the vagina was copious, commenced on the second day of life, persisted for 48 hours and was associated with bleeding from the cord and into the skin, and with a prolonged prothrombin time. Bleeding in the neighbourhood of the lachrymal duct in five infants was minimal in amount and consisted of a sero-sanguineous discharge appearing towards the end of the first week of life in two, and of a small haematoma occluding the lachrymal duct and noticed within 24 hours of birth in three babies. The sero-sanguineous discharges gave *Staphylococcus aureus* on culture, responded to local treatment and were the result of ascending nasal infection. Occlusion of the lachrymal duct by a haematoma contributed to unilateral excess lachrymation for a period of seven to 10 days pending the gradual spontaneous disappearance of the haematoma. There was no evidence of trauma, infection or bleeding elsewhere in these three cases.

*Superficial Laceration at Delivery* (7). Bleeding was accounted for by accidental incision of the scalp behind an ear in the course of delivery by caesarean section in three babies; and by infected lacerations of the scalp following the application of Willet's forceps in two infants. In a sixth infant the posterior aspect of the neck was deeply cut at the time of incision of the mother's undilated uterine cervix during delivery by the breech. The seventh case consisted of profuse bleeding from laceration of the frenulum of the upper lip as a direct result of the application of forceps. There was extensive bruising of the lip.

*After Circumcision* (12). The 12 infants were operated on on the seventh or eighth day of life. In five bleeding was arterial and ceased with ligation. Haemorrhage in a sixth infant was due to secondary infection with *Esch. coli*. There were two infants in whom an increased prothrombin time was associated with haemorrhage in other sites, and one in whom an increased prothrombin time was the only finding. Bleeding was unaccounted for in three babies, but ceased after the application of a local adrenaline dressing. The one instance of haemorrhage attributable to infection commenced 36 hours after operation, persisted for 48 hours but was not copious. In all the other 11 infants bleeding started suddenly within six to 17 hours of circumcision and when of arterial origin rapidly assumed considerable proportions. Two of the babies with arterial bleeding needed a transfusion.

*Bucco-nasopharyngeal* (13). Bleeding was from the nose in eight, the palate in three, and the pharynx in two babies. Epistaxis was moderately severe in five infants in all of whom the prothrombin time

was prolonged, but in only three of whom was there visible haemorrhage elsewhere. In the remaining cases bleeding took the form of blood-stained mucoid nasal discharge (present before nasal catheterization) in two infants with choanal stenosis and in one premature baby with severe congestive rhinorrhoea. The rhinorrhoea in this last infant was attributable to irritation by regurgitated gastric contents.

Palatal bleeding originated from a small ulcerative granulomatous lesion involving the soft palate in one infant, and in two other babies from minute, clearly defined ulcers with hyperaemic bases situated immediately adjacent to the median raphe of the mucous membrane lining the hard palate. The lesions in these three babies were noticed within 36 hours of birth, disappeared spontaneously within five to seven days and did not resemble Bednar's aphthae as described in the literature. There was no evidence of monilial, syphilitic or other local or general infection. Bleeding consisted of a persistent small loss sufficient to stain the salivary secretion. Abrasion of the mucous membrane by a mucus catheter accounted for bleeding from the pharynx in two babies. Haemorrhage was minimal and of short duration and caused less distress than the associated 'rasping', mildly stridorous spasmodic cough.

*Haemoptysis* (16). The details of babies with haemoptysis are summarized in Table 2. Copious haemoptysis was a terminal event in three babies with cyanotic congenital heart disease; three with gross developmental anomalies affecting both kidneys; two with signs of classical cold injury; and one with congenital thrombocytopenic purpura. Circulatory failure preceded haemoptysis in all nine of these cases. Haemoptysis occurred in two babies who showed evidence of severe intracranial irritation during life and who after death on the fourth and fifth days of life respectively were found at autopsy

TABLE 2  
HAEMOPTYSIS ACCORDING TO CAUSE (16 INFANTS)

Cause	No. of Infants
Terminal circulatory failure .. ..	9
Congenital malformation of heart .. ..	3
Congenital malformation of kidneys .. ..	3
Cold injury .. ..	2
Thrombocytopenic purpura .. ..	1
Asphyxia: intracranial haemorrhage .. ..	2
Staphylococcal pneumonia .. ..	2*
Septicaemia ( <i>Esch. coli</i> ) .. ..	1
Inspired blood following laryngeal intubation ..	1†
Prolonged prothrombin time; external bleeding elsewhere .. ..	1†

\* One survived.

† Survived.

to have extensive intracranial haemorrhage. In neither infant was the prothrombin time prolonged on the third day and in each the blood in the vomitus was foetal in character. Blood-stained mucus coughed up into the bucco-pharynx was a feature of two babies (of whom one survived) with staphylococcal pneumonia and of one infant with fatal coliform septicaemia. The bleeding in these three babies persisted for a number of days. Inhalation of blood, mild haemoptysis and stridorous cough followed trauma to the larynx at the time of resuscitative endotracheal intubation of one severely asphyxiated baby. This infant recovered, as also did one other in whom mild haemoptysis commencing on the third day of life and persisting for 24 hours occurred in the presence of simultaneous bleeding in other sites and of a prolonged prothrombin time.

Thirteen infants died.

**Superficial Trauma of Post-natal Origin (18).** Unavoidable trauma to superficially situated anomalous tissues accounted for bleeding in 11 babies. This applied to the gentle oozing of blood from the exposed surfaces of extensive meningocele (six) and more profuse bleeding from abrasion of large or multiple haemangiomas so situated that they could not be constantly and effectively protected from friction or pressure (three). Two infants had small circumscribed ulcer-like congenital defects of the scalp with vascular pericranial bases from which gentle oozing of blood took place over a period of 36 hours.

In another baby of not more than 30 weeks gestation, slight bleeding occurred from the base of a trophic ulcer which developed over the right parietal region in the third week of life. Haemorrhage from the lactiferous ducts in the two babies in whom it was noted was the direct result of what can only be described as ill-considered crude attempts at manual expression of the secretion from physiologically engorged breasts. Clinical evidence of secondary infection appeared within 48 hours. Deep, extensive excoriation of the perianal tissues following the persistent passage of frequent abnormal motions in two babies inadequately attended to at home was associated with slight but prolonged oozing of blood from the exposed inflamed surfaces. In another infant infection of an anal fissure was complicated by the development of a peri-anal abscess, the purulent discharge from which was heavily blood-stained and gave a mixed culture of *Esch. coli* and *Staphylococcus aureus*. Bleeding in the eighteenth case in the group was due to superficial erosion of a large teratoma originating in the inner canthus of one eye.

TABLE 3  
HAEMATURIA ACCORDING TO CAUSE (23 INFANTS)

Cause	No. of Infants
Septicaemia and/or pyelonephritis .. ..	8
Renal infarct(s) .. ..	7
Prolonged prothrombin time:	
haematuria only .. ..	2
haematuria and external bleeding elsewhere .. ..	2
Anomalies of kidneys and ureters .. ..	2
Ectopic bladder .. ..	1
Haemolytic disease .. ..	1

The six babies with meningocele and the one with teratoma died.

**Haematuria (23).** (Table 3.) In eight babies the haematuria was attributable to pyelonephritis, the infection being due to *Esch. coli* in five, *Staphylococcus aureus* in two, and undetermined in one. The renal condition was part of a generalized septicaemia in three of the cases due to *Esch. coli*. One of these three infants died. Hydronephrosis and hydroureter were features of two of the cases in which there was no evidence of septicaemia.

Renal infarction accounted for the haematuria in seven babies. In four instances haematuria synchronized with readily palpable clinical enlargement of one kidney. In each baby renal infarction occurred as a terminal event in the presence of a failing circulation. Four of the infants died from congenital heart disease, and death was contributed to by a combination of cardiac and renal anomalies in two other babies. The seventh baby with renal infarction died as a result of progressive emaciation in the presence of a meningocele and rapidly increasing hydrocephalus. Haematuria was present in two infants with anomalies of the ureters and renal pelves, which were radiographically demonstrated but apparently uninfected. Increased prothrombin time was a feature in four babies, in two of whom petechiae developed on the fourth day of life, together with melaena in one. The two remaining infants were examples of other forms of bleeding. In one, a rhesus baby, haematuria and cutaneous haemorrhages appeared within two hours of birth and before replacement transfusion; and in the other, oozing of blood from the exposed mucosa of an ectopic bladder persisted for a number of weeks after delivery.

**Cord/Umbilicus (26).** (Table 4.) Bleeding is best considered according as it occurred within a few hours of birth, some days after birth or with commencing separation of the cord. There were 11 instances of haemorrhage first detected within four to 12 hours of birth. Ligatures had been too loosely (six) or too tightly (two) applied in eight

TABLE 4  
BLEEDING FROM CORD/UMBILICUS ACCORDING  
TO CAUSE (26 INFANTS)

Cause of Bleeding	No. of Infants
<i>Soon after birth</i>	
Faulty ligation .. .. .	8
Hypodermic puncture proximal to ligature ..	2
Fistulous Meckel's diverticulum .. .. .	1
<i>A few days after birth</i>	
Infection .. .. .	3
Prolonged prothrombin time .. .. .	3
Prolonged prothrombin time; external bleeding elsewhere .. .. .	2
Uncertain .. .. .	1
<i>At time of separation</i>	
Meddlesome manipulation .. .. .	2
Excess granulation tissue .. .. .	2
Anomalous vascular supply .. .. .	2

babies: in two infants bleeding took place from the puncture site of resuscitative hypodermic injections given before ligation and proximal to the ligature level: and in the eleventh child external bleeding was the first indication of a fistulous Meckel's diverticulum.

Bleeding commencing three to five days after birth was associated with a prolonged prothrombin time in five and with secondary staphylococcal infection in three babies. There was bleeding in other sites in two of the infants with prolonged prothrombin time, and one of the examples of omphalitis occurred in a baby who recovered from severe cold injury. Haemorrhage on the fourth day of life in one baby was unexplained. Bleeding at a later period was attributable to meddlesome manual attempts to accelerate separation of the cord in two infants. Natural separation of the cord was complicated by haemorrhage in four babies, and was due to excessive amounts of proliferative granulation tissue at the base of the cord in two and to an anomalous arterial supply of the cord in the other two infants. The haemorrhage in the two last-mentioned cases was of sufficient severity to threaten life and necessitated surgical intervention.

Although there were no deaths, exsanguination needing immediate blood transfusion developed with dramatic suddenness in two infants in whom bleeding was due to faulty ligation.

*Cutaneous and Subcutaneous* (96). The evidence of haemorrhage consisted of numerous petechiae, extensive ecchymoses and contusions, separately or in combination. Instances of cephalhaematoma have not been included, as they were recorded as a routine only during the last year of the study. In that year, during which there were 1954 live births,

33 babies had *cephalhaematoma* of a size stimulating comment and 30 other babies had *subconjunctival haemorrhages*.

Numerous *petechiae* were the only finding in 17 babies of whom two were small premature and two large postmature infants. Delivery of one of the premature infants was by the breech. Of the 17 babies, three were asphyxiated at birth and two died as a result of massive suprarenal haemorrhage. The time of appearance of the petechiae varied. In nine infants it occurred within 24 hours of birth. These nine babies included five with haemolytic disease and the petechiae were present before replacement transfusion. The remaining eight babies with petechiae were examples of inoperable congenital atresia of the bile ducts (three), septicaemia (three), leukaemia (one) and thrombocytopenic purpura (one), and in them cutaneous haemorrhages first appeared in the second week of life or later.

*Ecchymoses* in the absence of other bleeding tendencies were present in 26 babies. In the majority the ecchymoses were detected at birth or within 24 hours of birth, but exceptionally they first appeared on the second or third day of life. Known local pressure, not invariably of abnormal degree, explained the bleeding in 14 of the babies, but in the remainder there was no convincing explanation. Of the 26 babies 17 were born to mothers with diabetes mellitus and all were premature; and of the remaining nine, four infants were delivered instrumentally after a prolonged labour, and two others were asphyxiated at birth.

Large *contusions* other than cephalhaematoma were a feature of 18 babies at or shortly after birth. In five cases the contusions merited the description haematoma. The presence of contusions was explained in every case by obstetrical complications. A breech presentation explained severe bruising of the external genitalia and/or perineum in seven babies. Similarly, the presenting structures were the site of contusions in five babies who presented either by the face or brow. Difficulty in delivering a limb accounted for extensive bruising of an arm in one infant and of a thigh in another. There was one example of bruising in the posterior thoracolumbar region due to difficulty in delivering the trunk because of a moderate degree of disproportion. In three babies extensive contusions involving the face coincided with the line of application of forceps blades. Of these three infants, two were delivered by the breech and one by the head.

The group of cutaneous and subcutaneous bleeding includes 35 infants exemplifying the condition sometimes referred to as traumatic cyanosis. From

the time of birth, or within one or two hours of birth, the head, face and neck were deeply cyanosed. The anatomical distribution of the cyanosis was characteristic and the line of demarcation between proximal cyanosed and distal healthily coloured tissues was clearly defined. The lips and buccal mucous membranes were not involved in the cyanosis. Numerous petechiae were irregularly but profusely distributed throughout the cyanosed surfaces of the face and scalp.

Of the 35 babies the birth weight of six ranged from 2 lb. 10 oz. to 5 lb. 3 oz., and of 29 from 5 lb. 14 oz. to 10 lb. Presentation was by the head, face and brow in 31, two and two cases respectively. Delivery of six infants was precipitate, being complete before arrival of the accoucheur in two; and labour was notably prolonged in the case of three infants. There were two instances each of rapid delivery of the head, slow delivery of the body, and of severe local pressure exerted by an umbilical cord tightly coiled round the neck.

The obstetrical histories of a number of the mothers were unusual. There were seven cases of pre-eclampsia with hypertension. Two mothers had severe mitral disease; one was a case of active pulmonary tuberculosis; another had an acute urinary infection; and yet another had viral pneumonia immediately before the onset of labour.

In this group of 35 infants there was a history of maternal antenatal ill health and/or an unusual feature in connexion with the labour or delivery in the case of no fewer than thirty. Severe post-natal asphyxia was present in 11 babies and convulsions occurred in two. Bradycardia during the first 48 hours of life was a feature of 10 of the infants, being associated with hypothermia in four. All 35 babies survived the first two weeks of life.

Cutaneous or subcutaneous bleeding was associated with haemorrhage in other situations in 22 babies. The prothrombin time was estimated in 15 of these infants and found to be prolonged in each case.

*Gastro-intestinal (155).* Loss of blood from the alimentary tract occurred in 155 babies. The clinical evidence of bleeding was melaena in 45, haematemesis in 36 and both melaena and haematemesis in 57 infants. There were 17 other babies in whom external bleeding in other situations was present in addition to melaena and/or haematemesis.

Table 5 analyses the clinical evidence of gastro-intestinal bleeding according to aetiology. Diagnosis in the two cases of gastro-duodenal ulcers was confirmed by autopsy findings, and in the two cases of hiatus hernia by observations during screening after oral barium. Haematemesis in the infants

TABLE 5  
GASTRO-INTESTINAL ACCORDING TO CAUSE  
(155 INFANTS)

Cause	No. of Infants
<i>Primary coagulation defect</i>	
Melaena .. .. .	28
Haematemesis .. .. .	12
Melaena and haematemesis .. .. .	37
Melaena and/or haematemesis and external bleeding elsewhere .. .. .	17
	94
<i>Swallowed blood</i>	
Melaena .. .. .	17
Haematemesis .. .. .	19
Melaena and haematemesis .. .. .	18
	54
Gastro-duodenal ulcers: melaena and haematemesis .. .. .	2
Hiatus hernia: haematemesis .. .. .	2
Pylorospasm: haematemesis .. .. .	1
Haemolytic disease: haematemesis-terminal .. .. .	1
Uncertain—? asphyxia: haematemesis .. .. .	1

with gastro-duodenal ulcers commenced on the first day of life, was copious and recurred at irregular intervals in the form of dark blood welling up in copious amounts. The appearance of melaena followed that of haematemesis in 12 hours in one baby and 30 hours in the other. In the infant with pylorospasm, diagnosis was based upon the presence of forceful vomiting, large amounts of mucus in the vomitus, a readily palpable contractile thickening of the pylorus and the rapid response to gastric lavage. The bleeding consisted of profuse streaking of the vomitus at the time when vomiting was most forceful, and was considered to be derived from gastric mucosa abnormally congested as a result of the vomiting. This case contrasted with 14 other infants in the total group of 155 (but not included in this section) in whom pylorospasm complicated copious haematemesis and was regarded as evidence of reflex response to the presence of a large amount of blood in the stomach.

Separation of the other examples of gastro-intestinal bleeding into the two groups of primary gastro-intestinal haemorrhage due to a coagulation defect and apparent haemorrhage secondary to the swallowing of maternal blood necessitated an analysis of the detailed recorded obstetrical, paediatric and laboratory findings.

A firm *diagnosis of primary alimentary haemorrhage* was made when blood lost was of foetal and not maternal type, and when there was significant prolongation of the prothrombin time. The otherwise unexplained presence of bleeding in other sites and the subsequent early appearance of a normocytic anaemia was accepted as corroborative evidence. Absence of any history of swallowed blood or blood-stained liquor and delay in the commencement of bleeding until the second day of life or after, provided further evidence in favour

of a diagnosis of primary haemorrhage. The haemorrhage was considered to be primary in origin in 94 babies.

Of the 94 infants 54 (57%) were born in hospital, 36 (38%) in their own homes and four (5%) in nursing homes; and 20 (21%) had a birth weight of 5½ lb. or less. Delivery was normal in 86 (91%), instrumental in seven (8%) and by caesarean section in one (1%); 90 infants (96%) were head and four (4%) breech presentations. There was one isolated example of ante-partum haemorrhage; and foetal distress or postnatal asphyxia or both were features of 13 (14%) deliveries. The forms of external bleeding in these 94 babies are given in Table 5. Bleeding was detected within 24 hours of birth in 17 (18%) of the 94 babies. Thirty-five (37%) were males and 59 (63%) females. Haemorrhage in other sites was a feature of 17 cases. There were two deaths in the 94 babies, the immediate cause being massive suprarenal haemorrhage in one and intracranial haemorrhage in the other.

Observations favouring a reasonably confident diagnosis of swallowed maternal blood included the suspected or observed swallowing of blood during or soon after delivery, the presence of blood-stained liquor amnii, a history of antepartum haemorrhage and/or delivery by caesarean section, no significant prolongation of the prothrombin time and determination of the lost blood as being of maternal type. Unexplained subsequent anaemia was unusual. Haematemesis when it is the only sign is more likely to be due to swallowed blood than primary bleeding, and this applies particularly to haematemesis which starts within 24 hours of birth.

In only two of the 54 babies regarded as having swallowed blood was the source of the blood not determined (Table 6). Fissures of the mother's nipples accounted for haematemesis in six breast-fed infants. In another baby, blood in the mother's milk was later found to be due to a carcinoma of

the breast. Antepartum haemorrhage was a feature of the delivery of 16 infants. The liquor amnii was noted as being blood-stained at the delivery of eight other babies. Five of these babies were delivered by caesarean section. Nineteen infants were observed to gasp and swallow blood-stained maternal secretions in the vagina before delivery of the head. Of these 19 babies five were delivered by the breech. There were in addition two prolonged labours, two precipitate deliveries and three instrumental deliveries. The cord was severed on account of shortness during the delivery of two infants. Possible sources of maternal bleeding included an episiotomy incision (three), lacerated cervix (two) and perineal tears (three). Among seven babies born at home, three were born before arrival of the accoucheur, one was delivered by the breech and birth of another was precipitate. Investigation into the circumstances of the delivery of the remaining two justified the assumption that the baby had probably inspired blood before being removed from the mother's labour bed.

Of the 54 infants, 35 (65%) were born in hospital and 19 (35%) in their own homes, and 14 (26%) had a birth weight of 5½ lb. or less. Delivery was normal in 31 (58%), instrumental in 11 (20%) and operative in 12 (21%). Forty-nine (91%) babies presented by the head and four (7%) by the breech. There was one example of transverse presentation. Delivery was preceded by antepartum haemorrhage in 14 (22%). Foetal distress or post-natal asphyxia or both were features in the birth of 35 (65%) of the babies. Twenty-six (48%) were males and 28 (52%) females. The forms of external bleeding in the 54 infants are given in Table 5. Bleeding was detected in 44 (81%) of the infants within 24 hours of birth. In no infant with haematemesis and/or melaena due to swallowed blood was there external bleeding in other sites. There was one death due to intracranial haemorrhage.

There was considerable variation in the time separating the appearance of swallowed blood as haematemesis and melaena in the same infant. This applied both to cases of primary haemorrhage and swallowed blood. The interval ranged from as little as two to as much as 48 hours. Delay in the appearance of melaena was most common in small premature infants. In them an odour of stale blood was sometimes detectable in advance of the appearance of blood in the motions; and in a limited number delayed or ineffective evacuation of blood from the intestine gave rise to abdominal discomfort, sometimes, but not invariably, associated with distension.

TABLE 6  
EXTERNAL BLEEDING IN THE NEWBORN:  
CIRCUMSTANCES CONTRIBUTING TO SWALLOWING OF BLOOD

Cause	No. of Infants
Breast feeding	
Fissuring of mother's nipples .. .. .	6
Bleeding from unsuspected mammary carcinoma .. .. .	1
Ante-partum haemorrhage .. .. .	16
Heavily blood-stained liquor amnii .. .. .	8
Aspiration of blood-stained maternal secretion in vagina .. .. .	19
Aspiration of blood on labour bed .. .. .	2
Not determined .. .. .	2
Total .. .. .	54

**The Aetiological Background.** Considering the various manifestations of bleeding in relation to contributory factors, haematemesis and/or melaena were explained by *swallowed maternal blood* in 54 cases.

**Trauma** in a variety of forms accounted for the bleeding in 42 babies, and at a conservative estimate contributed to bleeding in not fewer than 56 other infants. The application of forceps, abnormal presentations and abnormal uterine contraction were the cause of lacerations, severe contusions or haematomata in 24 infants; and there were four instances of accidental incision of the scalp or neck in the course of delivery. Haemorrhage was directly attributable to circumcision in five, and to traumatic procedures involving the cord in four infants. Limited bleeding followed the extraction of mucus in two babies and endotracheal intubation of another. Epistaxis complicated the violent spontaneous expulsion of a large tenacious plug of mucus from the naris of one baby, and a trophic or pressure ulcer of the scalp was the site of bleeding in one small premature infant. Trauma was only one of several factors contributing to traumatic cyanosis, occurring in circumstances which favoured local compression during delivery of the trunk, difficulty in delivering the shoulders and constriction of the neck by the cord.

**Infection** accounted for haemorrhage in 20 babies. The bleeding took place from the site of circumcision (one), the cord (three), the lachrymal duct (two), and the anus (one). Haemoptysis complicated staphylococcal pneumonia (two), haematuria was present in acute pyelonephritis (eight), and extensive petechial eruptions were a feature of septicaemia (three).

A variety of *developmental anomalies* contributed directly or indirectly to bleeding in one form or another in 30 infants. Terminal haemoptysis occurred in the presence of fatal congenital disease of the heart (three) and of the kidneys (three); and haematuria resulted from renal infarction in the presence of failing circulation due to congenital disease of the heart (seven). Slight haematemesis was a feature in two babies with hiatus hernia and slight epistaxis in two with choanal stenosis. Coozing of blood took place from a fistulous Meckel's diverticulum (one) and from the traumatized exposed surfaces of extensive meningomyeloceles (8x) and multiple large haemangiomas (three). Petechial eruptions developed as delayed manifestations in three infants with inoperable atresia of the bile ducts, complicated by cirrhosis and obstructive jaundice.

Bleeding in a further 106 babies was considered

to be due to a *disturbed coagulation mechanism*, in the absence of other discernible causes. The sites in which haemorrhage took place were gastro-intestinal (94), cutaneous and subcutaneous (22), the umbilical cord (five), the nasal passages (five), the renal tract (four), the vagina (two), and the respiratory tract (one). In addition, bleeding which followed the circumcision of three infants was thought to be due to the same cause. The two infants with vaginal haemorrhage represented the only two examples of severe bleeding from the vagina seen during the 11 years of the survey. Minimal physiological menstrual loss was a less frequent finding than expected and detailed observations conducted over a 12-month period demonstrated that it occurred in approximately 6% of liveborn female infants. In 24 of the 106 babies, external bleeding occurred more or less simultaneously in more than one situation (Table 7). Determination of a defective coagulation mechanism was based on prolongation of the prothrombin time in 77 of the 106 babies.

The age at onset of bleeding ranged from birth to 9 days, but was between 2 and 4 days in the case of 99 infants. Among the exceptions was one baby in whom bleeding from the cord commenced within 30 minutes of birth and persisted for four days; a second baby in whom melaena was present at the age of 10 hours; and two other infants in whom gastro-intestinal haemorrhage continued for several days after starting on the seventh and ninth day of life respectively. Another case of special interest was a baby in whom severe melaena ceased two days after commencement on the fourth day of life, only to recur on the thirteenth day and persist for 48 hours. Clotting and prothrombin times were prolonged in all four infants.

Prematurity was not a predominant feature of the group of babies with intrinsic gastro-intestinal haemorrhage. Of the 94 infants only 23% were of birth weight  $5\frac{1}{2}$  lb. or under, and 21% were

TABLE 7  
DISTURBED COAGULATION MECHANISM:  
INFANTS IN WHOM SIMULTANEOUS BLEEDING  
OCCURRED IN MORE THAN ONE SITUATION (24)

Sites of External Bleeding	No. of Babies
Gastro-intestinal: cutaneous .. ..	12
Gastro-intestinal: cutaneous: epistaxis .. ..	2
Gastro-intestinal: cutaneous: haematuria .. ..	1
Gastro-intestinal: cord .. ..	2
Cutaneous: vagina: cord .. ..	2
Cutaneous: circumcision .. ..	2
Cutaneous: epistaxis .. ..	1
Cutaneous: cord .. ..	1
Cutaneous: haematuria* .. ..	1

\* Subsequently died: massive suprarenal haemorrhage.

TABLE 8  
HAEMATEMESIS AND/OR MELAENA IN THE NEWBORN:  
MONTH OF OCCURRENCE

Month	Percentage of Infants With	
	Coagulation Defect (94)	Swallowed Maternal Blood (54)
January ..	11	9
February ..	15	9
March ..	11	11
April ..	5	6
May ..	10	8
June ..	6	11
July ..	8	9
August ..	3	4
September ..	4	9
October ..	9	6
November ..	4	9
December ..	14	9

TABLE 9  
FORM OF EXTERNAL BLEEDING IN RELATION TO CAUSE  
OF DEATH (52)

No. of Babies	Major Contributory Cause(s) of Death	Form(s) of External Bleeding
11	Congenital heart	Cutaneous (4) Haematuria (4) Haemoptysis (3)
6	Meningomyelocele: circulatory failure	Cutaneous (5) Haematuria (1)
6	Septicaemia	Cutaneous (4) Haematuria (1) Haemoptysis (1)
6	Prematurity: pulmonary disease	Cutaneous (6)
3	Renal anomalies	Haematuria and haemoptysis (2) Haemoptysis (1)
3	Cirrhosis: atresia of bile duct	Cutaneous (3)
2	Gastro-duodenal ulcers	Haematemesis and melaena (2)
2	Haemolytic disease	Cutaneous (2)
2	Cold injury	Haemoptysis (2)
2	Asphyxia: intracranial haemorrhage	Haemoptysis (2)
2	Asphyxia: suprarenal haemorrhage	Haematemesis and melaena (1) Cutaneous (1)
1	*Intracranial haemorrhage: asphyxia	†Haematemesis and melaena (1)
1	‡Intracranial haemorrhage: coagulation defect	Cutaneous (1)
1	Suprarenal haemorrhage: coagulation defect	Cutaneous (1)
1	Staphylococcal pneumonia	Haemoptysis (1)
1	Leukaemia	Cutaneous (1)
1	Thrombocytopenic purpura	Cutaneous and haemoptysis (1)
1	Teratoma	Cutaneous (1)

\* Massive subdural from tentorial tear.

† Maternal blood.

‡ Intraventricular and subarachnoid.

estimated as having a gestation period of less than 38 weeks. The corresponding percentages for the 54 babies with gastro-intestinal bleeding due to swallowed maternal blood were 26 and 28. Table 8 analyses the onset of haematemesis and/or melaena in relation to the months of the year. The figures suggest that in the winter there may be an increased incidence of these signs when attributable to a coagulation defect, but not when due to swallowed maternal blood.

### Deaths

There were 52 deaths in the total series of 345 cases. Details are summarized in Table 9.

### Discussion

The term 'haemorrhagic disease of the newly born' has lost some of its original clinical significance (Paterson and McCreary, 1956). Apparent bleeding from the gastro-intestinal tract of a newborn infant may be of maternal origin. Primary or intrinsic haemorrhage has to be differentiated from the so-called 'swallowed blood syndrome' (Apt and Downey, 1955; McKay and Smith, 1959; Sanford, 1961). Because of this, babies who vomited or passed blood of maternal origin *per rectum* have been included in the present study. They numbered 54. Twenty-three were originally diagnosed as suffering from haemorrhagic disease, the majority consisting of infants included in the early stages of the total series of 345 babies. Revision of diagnoses has taken account of subsequent experience gained with babies in whom routine investigations were extended to include estimation of prothrombin time and the differentiation of foetal from maternal blood.

**The Swallowed Blood Syndrome.** This term applies to the swallowing of maternal blood. It is evident from study of the 54 babies in the present series that maternal blood may be swallowed at any stage during labour and irrespective of whether delivery is spontaneous, instrumental or operative. The findings suggest that there is an especial liability in the presence of antepartum haemorrhage, and that there is always a possibility, after an episiotomy or where the cervix has been lacerated or the perineum torn. A breech presentation is associated with greater risk as the infant's first gasp may take place before delivery of the head. The likelihood of blood being swallowed is further increased when an unrelaxed cervix requires incision, or a short cord has to be severed during delivery.

The risks of blood being swallowed where there has been antepartum haemorrhage are not necessarily obviated by caesarean section. Difficulty in removing the infant from the uterus may stimulate early gasping movements with resultant swallowing of blood-stained liquor. Staining of the liquor with blood is not limited solely to operative deliveries carried out on account of antepartum haemorrhage; and the possibility of haematemesis or melaena in a newborn infant being evidence of swallowed blood should always be considered whenever delivery has been by caesarean section. The blood will almost certainly be maternal if the placenta has been inadvertently cut at the time of incision of the uterus.

Exceptionally the baby may swallow maternal blood after birth. Two instances occurred in the present series as a result of delay in removing the infant from the labour bed. Both infants were delivered at home in exceptional circumstances; both were born before arrival of the accoucheur, and in the case of one, anxiety concerning the mother diverted attention from the baby.

Haematemesis and/or melaena due to the presence of blood in the mother's milk was an infrequent finding. Usually blood from fissured nipples is present in the form of small clots and gives rise to haematemesis. By way of contrast, the ingestion of milk in which blood is more uniformly distributed is more likely to be followed by melaena than haematemesis. Of three such cases (of which only one is included in this study) seen by the writer, two were subsequently explained by mammary carcinoma, the third remaining undiagnosed.

Haematemesis due to maternal blood swallowed in the course of, or immediately after, delivery developed within two to 36 hours of birth, whereas that due to bleeding from fissured nipples commenced at some time after the fourth day of life.

**Visible Haemorrhage.** The different situations in which evidence of primary bleeding was encountered in 291 babies agree with those already reported in the literature (Stone, 1945; Wintrobe, 1951; Hughes, 1952; Sanford, 1961). There is general agreement that trauma, infection and congenital anomalies may contribute to haemorrhage.

**Routine Procedures.** Experience in the present series points to the necessity for being on the alert for bleeding after such routine procedures as circumcision, resuscitative mucus extraction and endotracheal intubation. Resuscitative measures are mentioned by Sanford (1961) as an occasional cause of bleeding, and Wintrobe (1951) describes

the bleeding following circumcision as being usually slow and unrelenting. Findings in the present study suggest that rapidly exsanguinating haemorrhage of sudden onset after circumcision and from the cord is not altogether uncommon. An incidental finding was that all the examples of exsanguination resulting from ineffective ligation of the cord occurred in hospital practice. A point of practical importance is that haemorrhage from the rectum can be caused by the careless use of a rectal thermometer. One such case not included in this study has been encountered.

**Traumatic Cyanosis.** Traumatic cyanosis is of special interest if only because of the multitude of overlapping potential contributory factors. There were 35 examples in the present series. Local compression was a feature in seven and foetal distress and/or severe postnatal asphyxia in 11 cases. Four infants showed evidence of severe intracranial irritation, two having convulsions. Of the mothers, no fewer than 12 required special care in the weeks immediately preceding parturition on account of pre-eclampsia (seven), heart disease (two) and active infection (three). Clifford (1939) emphasizes the importance of foetal distress and asphyxia as factors favouring neonatal haemorrhage and Jenny and Gschwend (1958) stress the causal significance of trauma, and capillary permeability and fragility in relation to petechial haemorrhages. In varying degrees anoxia, general circulatory stasis, impaired local venous return and increased capillary permeability were present in the 35 babies under consideration. Nor can the possibility of an associated coagulation defect be excluded in the absence of laboratory studies on these infants. It is not practicable in any general consideration of this subject to apportion particular emphasis to any one possible contributory factor. Nevertheless, in so far as a small number of cases warrants impressions, it appears that factors related to the antenatal health of the mother may be of no less significance than those connected with the mechanical circumstances of delivery.

**Infection.** Considering infection, haematuria due to secondarily infected hydronephrosis in this series was severe in contrast with Schaffer's experience (1960). Acute oesophagitis is described as a not uncommon cause and congenital syphilis as a rare cause of bleeding by Sanford (1961), but these conditions were not encountered. Other rare causes mentioned by Sanford (1961) are cytomegalic inclusion disease and toxoplasmosis. I have seen one example of each of these conditions and in each

(neither of which is included in this series) generalized petechiae were present at birth.

**Visceral Dysfunction.** Findings in this study differ from Schaffer (1960) in that haemolytic disease and haematuria were not features of infants with haemoptysis, and haematuria due to renal thrombosis was not invariably gross. Renal thrombosis can result from damage to the kidney during labour (Jenny and Gschwend, 1958; Schaffer, 1960) and has been seen by the writer, but did not occur in any baby in the present series. The occurrence of petechiae in association with disturbed liver function in newborn infants is well known (Poncher, 1942; Hughes, 1952; Paterson and McCreary, 1956; de Gruchy, 1960). Hepatic dysfunction may explain also the high incidence (33%) of bruising noted in macrosomic premature infants with large livers born to mothers with diabetes mellitus (Claye and Craig, 1959). There were two examples of gastro-duodenal ulcers, but none of intussusception or volvulus as mentioned by Sanford (1961).

**Prothrombin Levels and Prophylactic Vitamin K.** A question which inevitably arises is the extent to which this study lends support to prevailing views concerning the significance of the prothrombin level and the efficacy of vitamin K as a form of prophylactic and curative therapy. Poncher (1942) states that spontaneous haemorrhage does not occur and that there is a change in the integrity of the vascular wall in all cases of bleeding. He considers that this change may be due to trauma, venous congestion or anoxia and that the effect of a deficient clotting mechanism is to condition the severity of the haemorrhage. Both Poncher (1942) and Schaffer (1960) are of the opinion that no constant relationship exists between the prothrombin level and a liability to spontaneous bleeding, and Smith (1959) is not satisfied that there is as yet proof that a prolonged prothrombin time is an especial characteristic of prematurity. Nevertheless, Schaffer (1960) comments upon 'the virtual disappearance of haemorrhagic disease with the discovery that vitamin K accelerates the prothrombin time' and Waddell and Guerry (1939) report that not one case of haemorrhagic disease occurred in more than 4,000 newborn babies who were given vitamin K, or whose mothers were given the vitamin antenatally. All 22 premature babies in the group of disturbed coagulation mechanism in the present series were given 2 mg. of nikethamide shortly after birth. In addition, four babies born at term in nursing homes, who were transferred to hospital with severe haemorrhage, had, before the onset of bleeding, received vitamin K

in amounts which, today, would be regarded as injudiciously large.

On the assumption that a connexion exists between the prothrombin level and bleeding it has been postulated that the infrequency of bleeding after the fifth day of life can be explained by the bacterial synthesis of prothrombin which follows the oral intake of water or milk feeds (Poncher, 1942; Wintrobe, 1951; de Gruchy, 1960; Sanford, 1961). In the present group of 94 babies with primary gastro-intestinal haemorrhage all those born at term and in whom bleeding commenced after the second day of life had been given oral feeds at least 12 hours before bleeding appeared. Eighteen of the infants were recorded as having been put to the breast for more than 48 hours before the detection of haemorrhage, and six of these infants passed changing milk stools before the onset of visible bleeding. Together these findings justify some doubts as to whether, in fact, either feeds or vitamin K have a consistently significant preventive value. Antibiotics can interfere with the synthesis of vitamin K (de Gruchy, 1960). They were given to only one or two selected cases and cannot be considered to have confused the general impressions derived from this study.

**Vitamin K as a Curative Agent.** It is equally difficult to be wholly convinced concerning the curative potentialities of vitamin K. In inclining to this view, I am influenced by admittedly retrospective impressions of my mistaken confidence more than two decades ago in the routine use of intramuscular whole blood. I have records relating to the period 1932 to 1937 of 21 newborn babies to whom whole blood was given intramuscularly on account of haematemesis and/or melaena. There was one death attributable to uncontrollable haemorrhage from multiple gastro-duodenal ulcers. Allowing that in those days differentiation of foetal from maternal blood was not possible, and that the complications of the swallowed blood syndrome were not appreciated, the fact remains that deaths among infants with haemorrhagic disease, as the term was then used, were infrequent. Today the problem remains to know the frequency with which spontaneous arrest of bleeding would take place in the absence of vitamin or other therapy. My personal opinion is that most cases of true haemorrhage attributable to a defective coagulation mechanism would recover spontaneously. Wintrobe (1951) describes the condition as 'self-limited but sometimes fatal'. There can be no questioning the value of whole blood transfusion in dealing with threatening exsanguination. The rapid effect of transfusion

was a life-saving factor on five occasions in the present study.

The argument can be advanced that evaluation of vitamin K should take account of its value in preventing complicating, lethal deep or internal haemorrhage. Quick (1942) considers that many cases of intracranial bleeding are due to prothrombin deficiency. It is of significance that among the 52 babies who died in this total series of 345 infants, haemorrhage was the primary cause of death in only five (Table 9). There was laboratory evidence of disturbed coagulation mechanism in only two of these five infants—one infant who had petechial haemorrhage during life and who died as a result of intraventricular and subarachnoid bleeding; and another small premature baby with petechiae before sudden death from suprarenal haemorrhage. By way of contrast there was no prolongation of the prothrombin time in two asphyxiated infants with haemoptysis and intracranial haemorrhage; and in two babies with fatal suprarenal haemorrhage following gastro-intestinal bleeding in one and cutaneous haemorrhage in the other. A disturbed coagulation defect cannot be regarded as a prerequisite of simultaneous bleeding in more than one situation. The present study suggests that such bleeding is most frequently accounted for by circumstances favouring anoxia and that as previously stated (Craig, 1938) defects of coagulation are only very rarely of major importance in the causation of intracranial haemorrhage. Sanford (1948) states he has never seen a case of cerebral haemorrhage with coagulation dysfunction.

External bleeding in an infant is not of itself justification for attributing clinical signs of intracranial irritation to a bleeding tendency. In the present study fatal cerebral haemorrhage followed prolonged postnatal asphyxia in a baby who during life vomited blood which proved to be of maternal origin. Only examination of the blood established the true significance of the bleeding in relation to symptomatology. Moreover, as Wintrobe (1951) emphasizes, signs and symptoms due to intracranial haemorrhage differ little, whether due originally to trauma or to a bleeding tendency.

Again considering a possible relationship between the prothrombin level and apparent spontaneous bleeding, two findings require explanation. If a coagulation defect is the only aetiologically operating factor it is difficult to understand why simultaneous bleedings in multiple sites should not be of commoner occurrence as suggested by Quick (1942). External bleeding in more than one situation occurred in only 24 of the 106 cases of the group concerned in the present study. Equally perplexing is the

remarkably high incidence of haemorrhage from the gastro-intestinal tract—an observation recorded in many series (Poncher, 1942; Wintrobe, 1951; Dunham, 1955), but as yet never satisfactorily explained.

### Conclusions

External bleeding, although more frequently met with than internal haemorrhage, is relatively uncommon. It is important to remember that routine resuscitative and nursing measures are among the rare causes of bleeding.

In certain circumstances domiciliary care may favour the occurrence of traumatic bleeding because of unavoidable environmental handicaps in relation to delivery and subsequent care of the infant. This was evident in particular in connexion with superficially situated congenital anomalies. Of equal practical importance was the occurrence of haemoptysis in two small infants who developed cold injury some days after delivery at home. It is justifiable to draw attention to the fact that no fewer than 36 of the 94 babies with intrinsic alimentary bleeding were born in their own homes. If a relation exists between seasonal or environmental temperature and the occurrence of primary gastro-intestinal haemorrhage, the large number of domiciliary cases may reflect the effect of home conditions in a way analogous to that found in cold injury. The findings in the present series provide evidence also of the risks attendant upon birth of a baby in the absence of a professional attendant, circumstances virtually peculiar to domiciliary practice.

It should not be assumed, however, that inhalation of maternal blood after delivery occurs only in domiciliary practice. Albeit extremely rarely, it does occur in nursing homes and in hospital labour wards.

Moreover, another finding deserving mention is that the examples of exsanguination as a result of bleeding from the cord occurred in hospital. While this allows of no dogmatic conclusions it suggests at least that procedures undertaken by medical students and pupil midwives should be subject to the most careful supervision. On the other hand injudicious attempts to accelerate separation of the cord were encountered only in babies being delivered at home.

Hypothermia and sustained bradycardia with a sluggish circulation, separately or in combination, may increase the likelihood of bleeding in the presence of an additional contributory factor such as trauma or infection. The rarity with which external bleeding gives rise to an emergency situation is added reason for those responsible for the care of the newborn being trebly on the alert for the

exceptional situation. This applies particularly to routine periodical examination of the cord after delivery and the penis after circumcision. Premature babies should be kept under constant observation. They are unable to stand severe blood loss and the general systemic effects of severe haemorrhage are liable to be masked by frailty. Visible evidence of gastro-intestinal bleeding may afford no indication of the severity of the haemorrhage. Laboratory tests and consideration of the obstetrical history are essential in determining the source of blood in cases of haematemesis and melaena.

External bleeding is rarely fatal, but a confident prognosis must be based on the exclusion of coexistent deep internal haemorrhage. In the absence of explanatory trauma or infection, the aetiology of external bleeding often remains uncertain. As with so many other conditions in the newborn, bleeding may be the result of an aggravation of normal postnatal variations in the blood constituents. Just as the therapeutic use of vitamin K must be judicious so must the interpretation of the results of treatment. The many factors involved in the control of bleeding are only now being unravelled and current opinions concerning the value of vitamin K may have to be reviewed.

### Summary

A clinical study is presented of 345 newborn babies with external signs of bleeding, real or apparent.

Bleeding is discussed in terms of haematemesis, melaena, haematuria, haemoptysis, epistaxis, petechiae, ecchymoses, contusions or as haemorrhage following circumcision or from the cord.

The aetiological significance of trauma, infection, congenital anomalies and defective coagulation mechanism of the blood is considered.

The circumstances in which haematemesis and melaena may be due to swallowed maternal blood are reviewed.

It is considered that maternal factors may influence the occurrence of traumatic cyanosis.

Observations lend support to the view that the incidence of intrinsic gastro-intestinal haemorrhage

is subject to seasonal variations, but do not confirm that the condition is found most commonly in premature babies.

Reasons are advanced for questioning the value of vitamin K therapy in the prophylactic and curative treatment of primary intrinsic gastro-intestinal haemorrhage of the newborn.

Attention is drawn to circumstances of hospital and domiciliary practice with a bearing on bleeding in the newborn.

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# BRONCHIECTASIS

## A LONG-TERM FOLLOW-UP OF MEDICAL AND SURGICAL CASES FROM CHILDHOOD

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Over the past 30 years the natural history of bronchiectasis must have been considerably modified by the varying treatments which have been introduced. Laennec's original description in 1829 was made from post-mortem material, the diagnosis in those early years only being made in severe clinical cases or at autopsy. With the introduction by Sicard and Forestier in 1922 of an opaque substance to outline the bronchial tree, more accurate diagnosis was possible, but whilst this new diagnostic technique was being improved, measures to combat the disease were introduced. Physiotherapy with postural drainage and breathing exercises was soon assisted by the introduction of chemotherapy and antibiotics. At about the same time surgical procedures, i.e. lobectomy and pneumonectomy, were adopted and later multiple segmental resections were practised in an attempt to remove, if possible, all the diseased parts. But it was soon realized that bronchiectasis was not just an anatomical dilatation of certain bronchi, but usually a general disease complex, and removal of all diseased parts did not necessarily relieve all the symptoms. As a result surgery was recommended less and less, particularly as chemotherapy was able to control the respiratory exacerbations.

The present survey of 225 patients observed over a period of eight to 21 years covers this period of changing conditions. In most cases the diagnosis was made before the introduction of antibiotics and in some cases before the use of sulphonamides. In spite of the varying treatments a definite pattern of disease seems to emerge in which the onset of damage to the lung is maximal in the first five years of life. Thereafter the symptoms may be troublesome until puberty, when a surprising improvement in health occurs, lasting usually through the 'teens

into the twenties. It remains to be seen what happens in later life.

Earlier studies on these patients were reported in 1949 (Field) and the present study is a continuation of this work.

### The Present Study

This report consists of 104 patients treated medically and 121 treated surgically. Although the author has been in Singapore for the past 11 years, contact with the patients was made on each home leave, and in 1956 137 patients were asked to attend for a clinical examination; 84 attended and 25, who were unable to attend, replied to a special questionnaire. There was no reply in 28 cases, usually because they had moved and the address was unknown. Out of these 109 patients, four were surgically treated and have been included in the surgical series and one who had died eight years previously was excluded, thus leaving 104 patients who constitute the medically treated patients of this study. All of these had at one time shown some dilatation of the bronchi by bronchogram, but in 38 instances this was mild and of doubtful permanency. All had symptoms of chronic chest disease.

Most of the surgical patients had been operated on by Professor R. S. Pilcher and his staff, and were being followed up regularly in his clinic. With his kind co-operation a special questionnaire was filled in by the patients when they attended the clinic and the examining doctor filled in the clinical record. A full record was obtained of 117 cases out of 150, and with four patients who had had operations from the medical clinic there were 121 surgically treated patients. In no way can this surgical series be compared with the medical series as selection for operation is essential, but the two records are given side by side. No attempt has been made to grade the severity of the bronchiectasis as this study is

\* Address from May 1962: The Paediatric Unit, Queen Mary Hospital, Hong-Kong.

DURATION OF FOLLOW-UP

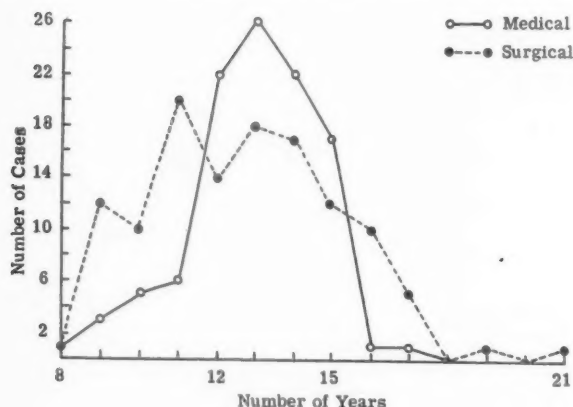


FIG. 1

AGE OF PATIENTS AT 1956 SURVEY

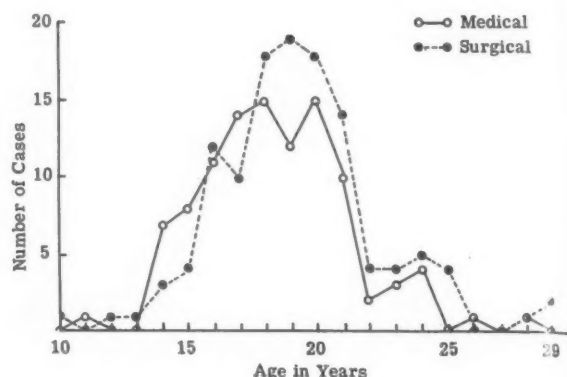


FIG. 2

SITE OF DISEASED BRONCHI

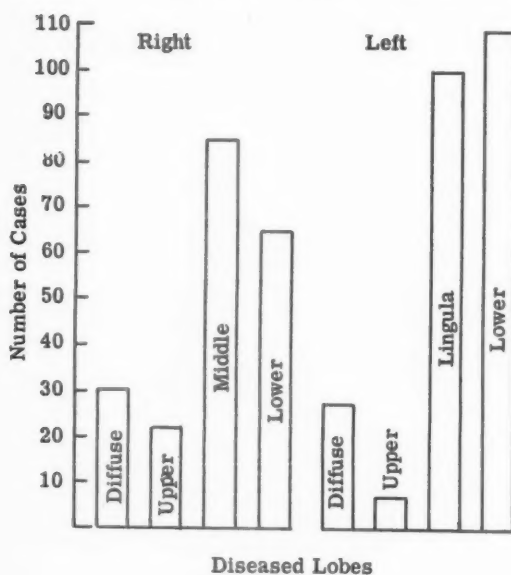


FIG. 3

TABLE 1

PERCENTAGE INCIDENCE OF TYPE OF BRONCHIECTASIS

Type	Per cent.
Tubular .. ..	35
Saccular .. ..	30
Varicose .. ..	27
Fusiform .. ..	11

more one of progress of the disease itself. There was no selection of cases at the onset; all cases who showed dilatation of the bronchi and who attended the children's Chest Clinics at two London hospitals over a period of several years were included. There were, however, different observers for the medical and surgical follow-ups.

**Duration of Follow-up.** It will be seen from Fig. 1 that the minimum number of years for which the patients have been followed is eight years and the maximum 21 years; the majority have been followed for 11 to 15 years.

**Age.** The majority of patients during the 1956 survey were between the ages of 14 and 24 years, the youngest being 10 years and the oldest 29 years (Fig. 2).

**Sex.** There are 102 males and 123 females; this supports the common finding of a slight preponderance of females.

**Site of Disease (Fig. 3).** As previously recorded (Field, 1949) the left lower lobe and lingula of the left upper lobe are most frequently affected, followed by the right middle lobe. In this series the right lower lobe is not quite so frequently affected.

**Type of Bronchiectasis.** Four types of bronchiectasis are described, but there are many variations of these and more than one type can be seen in one patient (Table 1).

Tubular dilatation is often the early stage of the disease in children, and this explains the high incidence. As the terminal part distends and becomes more bulbous, the bronchiectasis becomes

TABLE 2  
AGE OF ONSET AND NUMBER OF CASES

Age of Onset	Number of Cases
First 12 months .. ..	50
1 year-5 years .. ..	119
5 years-10 years .. ..	51
10 years-15 years .. ..	3
No record .. ..	2

saccular in type. Varicose has been used here to describe the irregular dilatations along the length of the bronchus, and fusiform, the dilatation which is most marked in the middle of the bronchus (Field, 1949). The varicose and fusiform types usually have a good prognosis.

Children were only seen up to the age of 12 years in the chest clinics, but the figures in Table 2 show that the dangerous period is in the first five years of life, when 75% of the cases occurred.

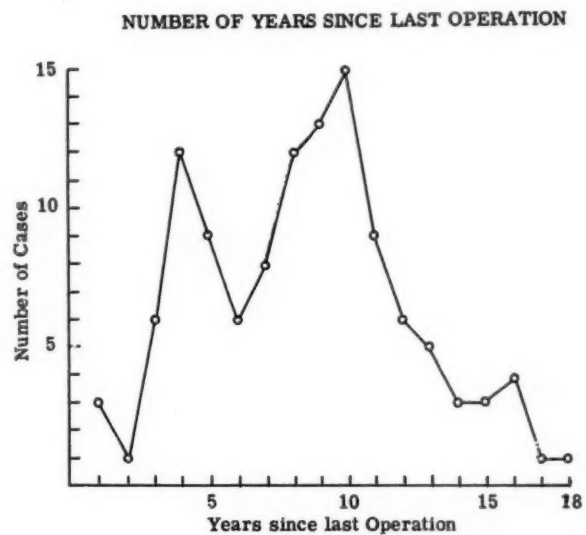
**Clinical Features.** Although careful records were kept from the beginning of this study, it was only after several years that the importance of certain clinical features was recognized and recorded; the clinical records for these features, therefore, are inadequate for when the patients were first seen. However, where it is helpful, the records available will be shown. For the more important symptoms such as cough, sputum, nasal discharge, clubbing and moist sounds in the lungs, the early records are reasonably adequate, but where no record was available this is recorded.

**Treatment.** The medically treated patients received no special treatment; the majority had given up postural drainage and they were on no regular treatment. Antibiotics were usually given

by their own doctors for exacerbation of chest symptoms, but as far as I know none of them received continuous chemotherapy.

**Pulmonary Resection.** As might be expected, the lingula of the left upper lobe, the right middle lobe and the left lower lobe were the most frequently removed lobes of the lung; partial resection of a lobe was also performed not infrequently (Table 3).

**Duration since Last Operation (Fig. 4).** The majority of patients had their operation between three and 12 years ago, although three cases had a further operation only one year before clinical assessment.



#### Results of the Follow-up

**Clinical Impressions.** In the past, before statistical evidence was considered so necessary, great importance was attached to a good clinical description of a disease or disease process. At present clinicians find it necessary to prove their point statistically before it is accepted. Studying the present figures after the follow-up clinics in 1956 I realized how inadequate such figures were to express the clinical change that takes place in these bronchiectatic children. Therefore, before attempting to give the results of this investigation, I shall briefly describe my own clinical impressions of the disease process.

The bronchiectatic process most commonly commences in infancy as a result of chest infections, particularly pneumonia, measles or whooping cough; thereafter the child suffers from recurrent

TABLE 3  
SITE OF PULMONARY RESECTION\*

Site of Resection	Number of Patients	
	Right Lobe	Left Lobe
<b>Upper lobes</b>		
Complete .. ..	4	12
Segmental-antero-lateral .. ..	16	9
Segmental-apical .. ..	2	0
Segmental-postero-lateral .. ..	0	0
<b>Middle and lingula lobes</b> .. ..	67	72
<b>Lower lobes</b>		
Complete .. ..	20	56
Partial-anterior basic .. ..	16	7
Partial-middle basic .. ..	4	1
Partial-posterior basic .. ..	1	4
Partial-dorsal .. ..	10	8

\* Multiple resections account for high total figures.

bronchitis, often with an asthmatic wheeze, running nose and usually a persistently infected lung, as shown by a cough and moist sounds in the lung. At this age the disease process often seems to be generalized and is difficult to define. Recurrent pulmonary collapse is a common feature.

From 6 to 12 years of age the child's condition improves a little, although the cough usually persists often with a nasal discharge and sputum may be produced. Attacks of recurrent bronchitis or asthmatic bronchitis become less frequent and recurrent pulmonary collapse is less commonly seen.

As puberty approaches, a remarkable change seems to take place. No longer is the child anxious or worried about his disorder; many lose their cough and symptoms, and if they persist they cause little discomfort. Even their parents stop worrying about them. Their whole outlook on life has changed and their disease is quite a secondary matter. Clubbing usually disappears and moist sounds in the lungs are far less frequent. This is the picture of the mild and moderate case. The more severe cases are a little different. They usually persist with a cough which, however, becomes less troublesome; sputum may persist, but does not increase in quantity as might be expected, although some do complain of streaks of blood in the sputum.

On the whole the activity of the bronchiectatic adolescent is not impaired; most of them lead a reasonably full active life, but some complain that running makes them cough and they avoid it. The majority take jobs of one sort or another; most of these were either sedentary in nature or only required moderate exercise; but some preferred an open-air job. Many are now married, and none complained that their disease was a bar to marriage, although in a surgical case there has been one marital complication since marriage due to the danger of having further children. Reproduction appears to be normal, but growth as measured by height and weight does seem to be slightly impaired (see Figs. 6 and 7).

One small group in which diffuse bronchiectasis is associated with moderately severe asthmatic symptoms improve very little. Clubbing usually persists and the lungs are rarely clear of moist sounds; growth is stunted and there is often slight cyanosis showing the extent of lung damage, and they are unable to do a full-time job because of fatigue. The three cases in this category all died between the ages of 17 and 21 years from pulmonary insufficiency with signs of cor pulmonale. There have been eight deaths in the series since this study was first reported in 1947 (Field, 1949) and four more since 1956. These are reported in detail later.

Pulmonary resection undoubtedly improves certain cases if carefully selected for operation and relieves some of the most severe cases of many of their symptoms, but it does not seem to affect to any great degree the natural history of the disease. Bronchiectasis is so often something more than just localized damage to bronchi: it is a generalized respiratory disorder with a susceptibility to recurrent chest infections, sinusitis and their accompaniments, including allergy, and it is this that may persist in spite of surgical removal of the diseased parts. The patients treated surgically improved at puberty and during their teens, as did the patients treated medically, but they continue to have recurrent chest infections and there seems to be little to choose between the two groups.

Recurrent or persistent nasal infection and sinusitis is probably as troublesome to a bronchiectatic as his chest infection and it is often difficult to clear. This may account for some of the persistent symptoms.

Practically all the cases with recurrent pulmonary collapse showed, at a later date, typical asthmatic symptoms suggesting that the cause of recurrent pulmonary collapse is most commonly allergic in nature. Eight out of nine of these cases appeared to be quite well by puberty.

This story so far is only half told, for as the adolescent merges into adult life with marriage, children and responsibility some of the symptoms return and become troublesome, constituting what is commonly known as recurrent or chronic bronchitis in adults. As the follow-up continues it is my impression that the symptoms become more troublesome.

The exact part that *chemotherapy* and *antibiotics* play in the modification of the natural history of this disease is very difficult to assess. At the beginning of this study even the sulphonamides were not in general use and most of the cases were selected before chemotherapy could have had much influence. However, there is no doubt that antibiotics play an important part in the recurrent chest infections and reduce the dangers of complications in surgery so that their use must have affected to some extent the prognosis; it is doubtful if it has affected to any great degree the prevention of recurrent chest infections. As far as I know continuous chemotherapy has not been used on any of these children. It seems, therefore, that the natural history of bronchiectasis continues as before with modifications due to the use of antibiotics during respiratory exacerbation, which probably slows down quite considerably the deterioration that may occur in the more severe cases. The use of anti-

MEDICAL ASSESSMENT OF PROGRESS

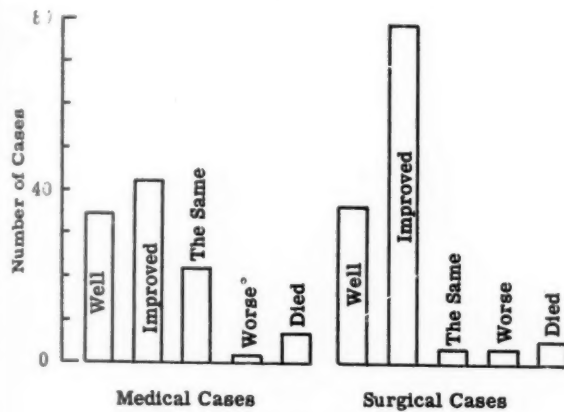


FIG. 5

biotics is probably not responsible for the great improvement seen at puberty in this series of cases; it seems that this has been and is the natural process of the disease. I am unable to give a satisfactory explanation, but there are three possibilities:

- An endocrine influence.
  - Anatomical growth of bronchi and muscles, resulting in better expulsive power and drainage.
  - Psychological: the adolescent usually has so many absorbing interests that health becomes of secondary importance; they also tend to look at life through rose-tinted spectacles.
- I do not think (c) can account for all this change which is probably a combination of many factors.

Bronchiectasis in association with tuberculous hilar glands is often slow in developing and causes fewer symptoms. It is usually in the upper lobes when it is doubtful if pulmonary resection is justifiable as symptoms are few or absent. When it occurs in the middle or lower lobes and produces symptoms, pulmonary resection is advisable. It seems that bronchiectasis following tuberculosis is less troublesome.

**Analysis of the Results.** In an attempt to prove the clinical impressions just recorded, the following data were compiled from the records kept in 1956 of 104 patients treated medically and 121 patients treated surgically, who were followed up for eight to 21 years.

**General Assessment** (Fig. 5 and Table 4). When all the data had been collected a general assessment of progress was made by the doctor.

Only four children have deteriorated and four have died, although the condition of 22 medically

TABLE 4  
DATA FOR FIG. 5

Assessment of Progress	Number of Cases	
	Medical	Surgical
Well .. .. .	35	36
Improved .. .. .	42	79
The same .. .. .	22	3
Worse .. .. .	1	3
Died* .. .. .	4(+3*)	0(+5*)

\* See under Deaths.

treated patients, as opposed to only three surgically treated patients, remained the same. The number of deaths gives a deceptive impression as those children known to have died before the 1956 survey were not included in the survey, but are fully reported later in this paper and included in Fig. 5.

**Intercurrent Illnesses** (Table 5). Bronchitis is the most frequent and troublesome complication which usually, however, responds well to antibiotics. About 50% of the patients have suffered from an intercurrent chest disorder.

TABLE 5  
NUMBER OF PATIENTS SUFFERING FROM INTER-CURRENT ILLNESS DURING THE PAST SIX YEARS

Illness	Patients Treated Medically	Patients Treated Surgically
Pneumonia .. .. .	14	8
Bronchitis .. .. .	28	47
Asthma .. .. .	14	8
Miscellaneous .. .. .	33	22
None .. .. .	39	19*
No record .. .. .	3	26*

\* Surgical patients with no illness were often not recorded so that many cases under 'No record' could really be under 'None'.

**Time Off Work or School** (Table 6). Twelve medical patients with over 16 weeks' sick leave indicate that the more severe cases are incapacitated; three of these cases died shortly after these records had been collected. In about 50% of the

TABLE 6  
NUMBER OF WEEKS SICK LEAVE DURING THE PAST SIX YEARS (EXCLUDING OPERATIONS)

Sick Leave (weeks)	Patients Treated Medically	Patients Treated Surgically
None .. .. .	27	21
1-2 .. .. .	27	38
3-4 .. .. .	17	23
5-8 .. .. .	13	11
9-16 .. .. .	4	14
> 16 .. .. .	12	6
No record .. .. .	4	8

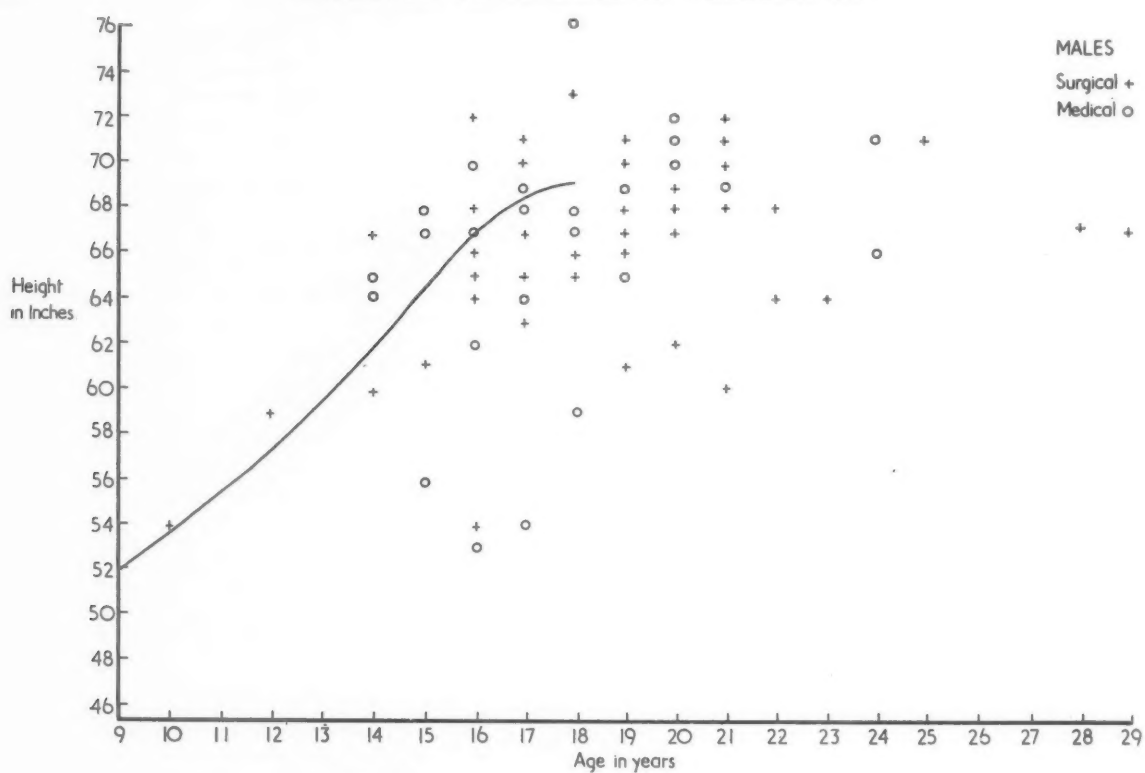


FIG. 6a.—Heights in males related to 50th percentile.

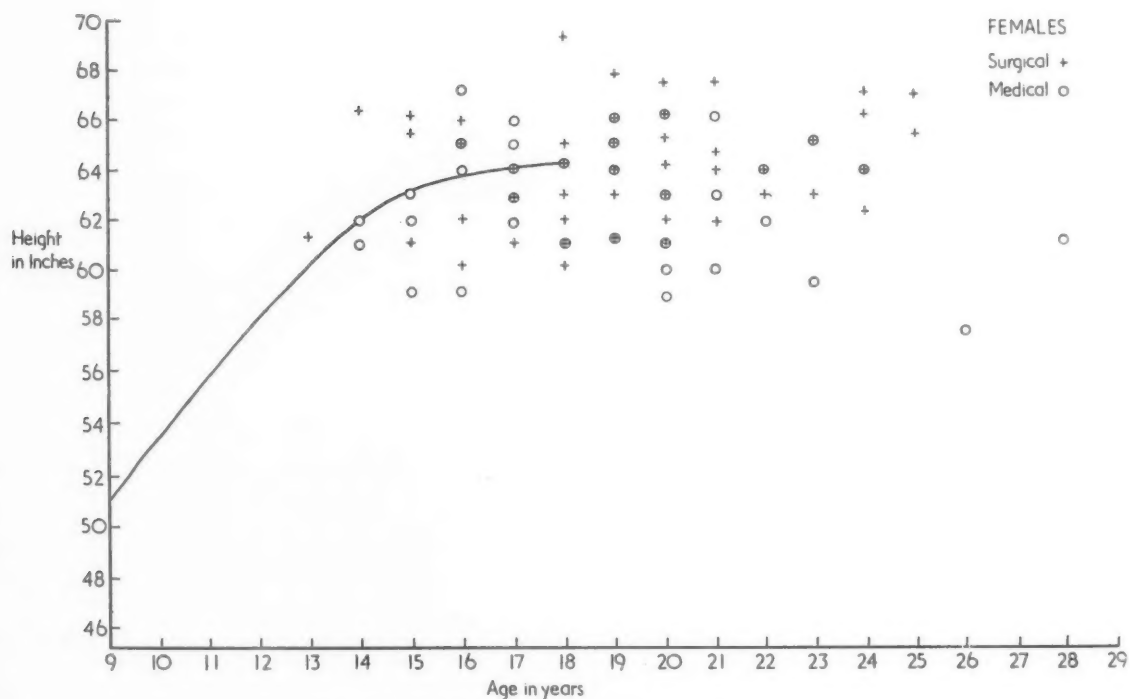


FIG. 6b.—Heights in females related to 50th percentile.

# BRONCHIECTASIS

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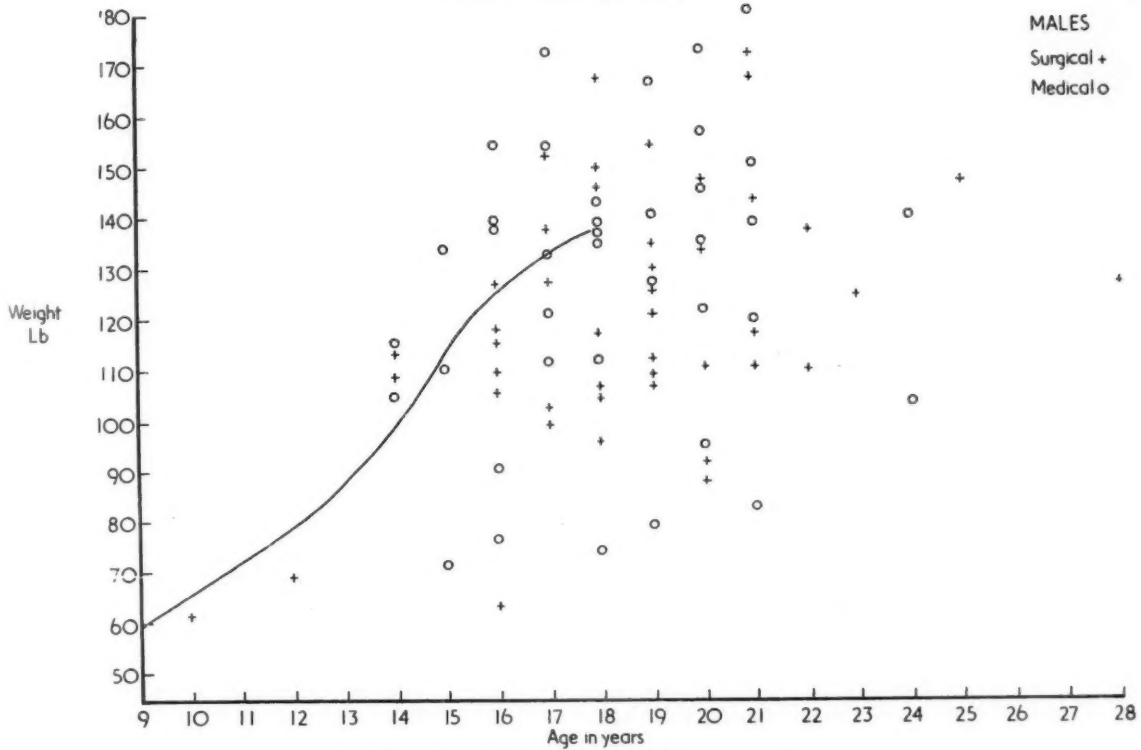


FIG. 7a.—Weight in males related to 50th percentile.

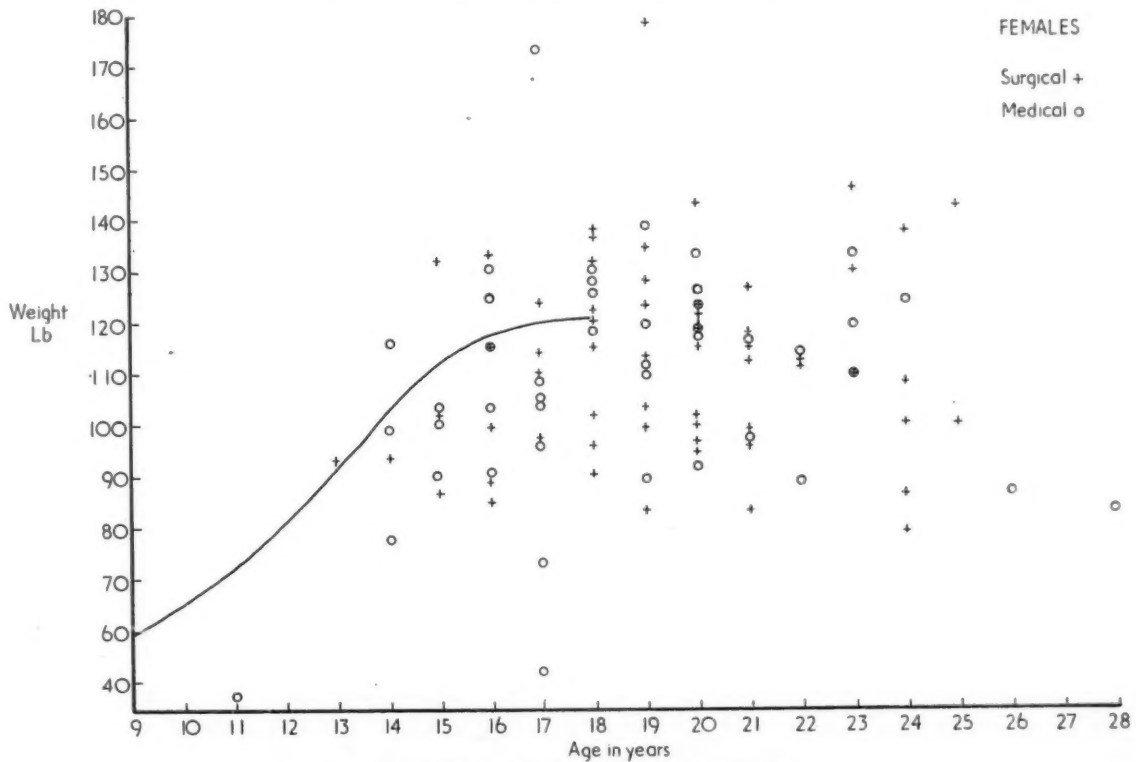


FIG. 7b.—Weight in females related to 50th percentile.

TABLE 7

PATIENT'S ASSESSMENT OF HIS HEALTH DURING THE PAST SIX YEARS

Assessment	Patients Treated Medically	Patients Treated Surgically
Improved .. ..	84	93
The same .. ..	12	19
Worse .. ..	3	3
No record .. ..	5	6

cases the cause for sick leave was connected with the chest.

*Patient's Assessment of His Health* (Table 7). Each patient was asked whether he felt his condition had improved over the past six years or was the same, or whether it was worse.

This assessment is similar to the evaluation of the doctors shown in Fig. 5; the vast majority say they feel better.

*Marriage.* When these records were compiled in 1956, nine medical and 14 surgical patients were married with an aggregate number of 18 children between them. The health since marriage of 11 had improved and of 10 was the same; nobody was worse, but there was no record for two. One patient now living in Canada informs me that the doctor has advised her against having further children and recommends sterilization. This has caused difficulties in the family. The patient, now aged 29 years, always rather fragile, was one of the early surgical cases in which the right middle lobe, left lower and lingula lobes were removed, and the left upper lobe failed to expand and finally had to be removed. She has therefore reached the age of 29 years (at the time of writing), has been married for eight years, and has had one child, with only the upper and lower lobes of the right lung.

It is too early at this stage to give a report on the effect of marriage in these patients. Many more are now married and further records may be revealing.

*Clinical Assessment.* Although careful records were kept at the beginning of this study, the importance of certain clinical features was not realized till later and the records are incomplete. Usually, if no record was made, it meant the symptom was not present, but this cannot be assumed. In the important features the records are reasonably complete and will be recorded.

*Growth and Nutrition.* Figs. 6 and 7 show the individual records for height and weight in relation

to age and in relation to the average 50th percentile. It will be noted that more patients in all charts are below the 50th percentile than above it and some patients, particularly those treated medically, are quite severely undersized. It had been noted that the severe cases, particularly those with asthma, were stunted, but the general tendency for the bronchiectatic to be undersized was a surprise finding.

*Cough.* Fig. 8 and Table 8 show clearly that the severity of the cough has improved over the years and 44 medically treated patients and 31 surgically treated patients are now free from cough. When it is present it is far less persistent than in childhood.

*Sputum.* Unfortunately early records are incomplete, but data in Fig. 9 and Table 9 show a tendency to lessening of the amount of sputum. Haemoptysis was rare in infancy, but streaking of sputum with blood was noticed in a few patients during adolescence. One patient died of a severe haemoptysis.

*Nasal Discharge.* Two records were kept of nasal discharge: the patient's complaint and the doctor's observation. The simple clinical test of blocking each nostril separately with the finger and asking the patient to sniff was applied.

Figs. 10 and 11 and Tables 10 and 11 show that there was a definite improvement in the nasal discharge during adolescence both as a symptom and as a clinical sign. Many of these children had sinus operations in childhood. It seems that the sinus infection is as troublesome as the chest infection in many of these patients and probably accounts for some of the sputum.

*Wheezing.* In children this is often associated with respiratory infection and seems to be less marked as the child grows older. Early records are incomplete, but the 1956 records (Table 12) show that a number still suffer from this complaint occasionally.

*Breathlessness.* This is a vague and ill-defined symptom and early records are incomplete. In the 1956 survey there were many, particularly in the surgical group, who said they became breathless on exercise (Table 13). This is of no significance without further tests, but is something which might be investigated.

*Clinical Signs.* For those patients who were unable to attend for a clinical examination but replied to a questionnaire, no clinical records were obtained. However, one patient had been examined

SEVERITY OF COUGH  
(Combined Medical & Surgical Cases)

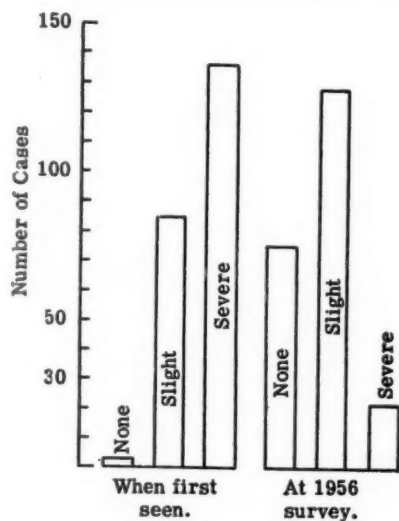


FIG. 8

TABLE 8  
DATA FOR FIG. 8

Severity of Cough	Number of Cases		
	When First Seen	1956 Survey	
None .. ..	3	44	31
Slight .. ..	83	47	81
Severe .. ..	136	12	9
No record ..	3	1	0

AMOUNT OF SPUTUM  
(Combined Medical & Surgical Cases)

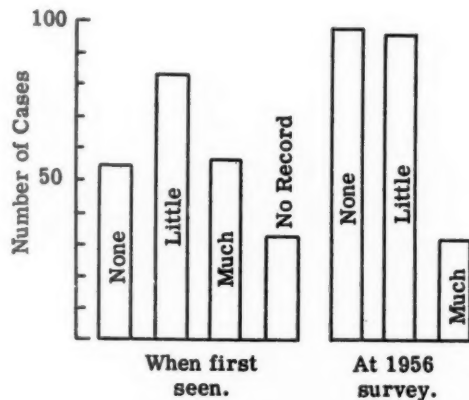


FIG. 9

TABLE 9  
DATA FOR FIG. 9

Amount of Sputum	When First Seen	Number of Cases	
		1956 Survey	
		Medical	Surgical
None .. ..	55	48	50
Little .. ..	82	38	58
Much .. ..	56	18	13
No record ..	32	0	0

NASAL DISCHARGE  
AS A COMPLAINT BY THE PATIENT

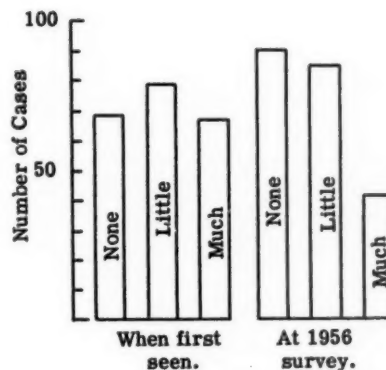


FIG. 10

TABLE 10  
DATA FOR FIG. 10

Complaint of Nasal Discharge	When First Seen	Number of Cases	
		1956 Survey	
		Medical	Surgical
None .. ..	69	47	43
Little .. ..	79	33	52
Much .. ..	67	21	20
No record ..	10	3	6

two years previously and 14 patients three years previously, and these clinical records were accepted. In a few patients a clinical report was obtained from the private practitioner.

Early records are incomplete except for clubbing and moist sounds in the lungs.

*Posture, Shape of Chest and Chest Expansion.* Postural defects are not uncommon, particularly round shoulders, protuberant abdomen and lordosis, and these do not seem to improve during

### NASAL SECRETION AS NOTED BY THE DOCTOR

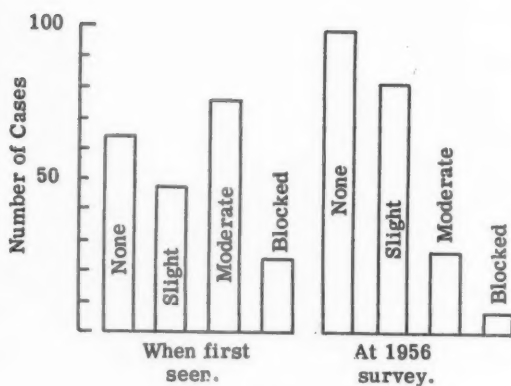


FIG. 11

TABLE 11  
DATA FOR FIG. 11

Observed Nasal Secretion	Number of Cases		
	When First Seen	1956 Survey	
		Medical	Surgical
None .. ..	63	44	55
Slight .. ..	48	35	48
Moderate ..	76	13	14
Blocked .. .	23	5	2
No record ..	15	6	5

TABLE 12

### WHEEZING AS A SYMPTOM IN THE FOLLOW-UP RECORDS OF 1956

Symptoms of Wheezing	Patients Treated Medically	Patients Treated Surgically
None .. ..	60	65
Little .. ..	32	43
Much .. ..	10	10
No record ..	2	3

TABLE 13

### BREATHLESSNESS AS A COMPLAINT IN THE FOLLOW-UP RECORDS OF 1956

Breathlessness	Number of Patients	
	Medical	Surgical
None .. ..	50	45
On exercise ..	48	71
At rest .. ..	3	2
No record .. .	3	3

adolescence. Postural defects after pulmonary resection, particularly curvature of the spine and flattening of one side of the chest, may also persist. Sometimes flattening of the chest follows pulmonary collapse. Pigeon chest was most commonly seen in those children with associated asthmatic symptoms. Tables 14 and 15 illustrate the prevalence of chest deformities.

*Chest Expansion* (Table 16). The greater number with 'good expansion' in the surgically treated patients is probably the result of breathing exercises which are practised more diligently after surgery. Very few medically treated patients persisted with the breathing exercises.

*Clubbing*. In bronchiectasis, clubbing usually indicates a purulent infection of the chest. With the use of antibiotics the infection has come under control and the clubbing has disappeared, as it has also after surgical removal of the diseased part. Fig. 12 and Table 17 show the disappearance of clubbing in about one-quarter of the cases.

*Moist Sounds in the Chest*. Moist sounds in the lungs are usually indicative of some persistent infection or allergy. Fig. 13 and Table 18 show the tremendous improvement in both medically and surgically treated patients in adolescence; in 129 patients no moist sounds were heard in the follow-up survey.

At the onset of the disease râles were more in evidence than rhonchi, and in the follow-up they were of equal prevalence.

*General Comments on Clinical Features*. These records support the clinical impressions of a subjective and actual improvement in the average case of bronchiectasis during adolescence. The cough, sputum, clubbing and moist sounds in the chest all improve, although nasal secretion continues to be troublesome and posture may remain defective.

*Bronchographic Changes*. Repeat bronchographic studies have not usually been done on these children during adolescence; nevertheless, certain changes have been observed over the years in specific cases.

As already stated, the fusiform and varicose types of bronchiectasis usually have a good prognosis. The saccular type is variable, depending on the extent of the disease and the associated damage to the bronchi. The patient continues to have a cough with sputum and some of these have persistent clubbing. The tubular type of bronchiectasis shows definite changes over the years and in itself it is

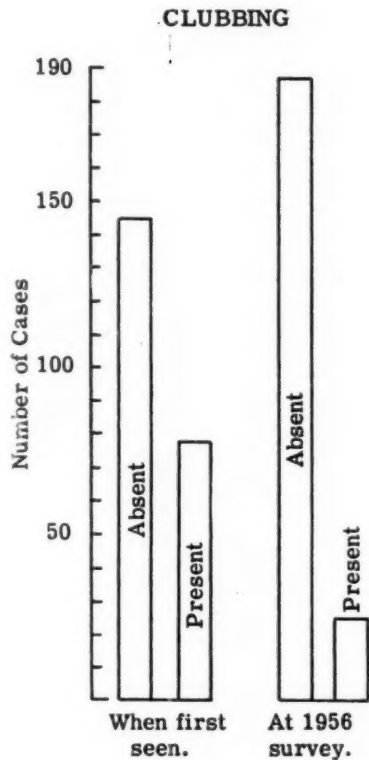


FIG. 12

probably not a stable form. Three changes have been noted.

1. The bronchi revert to normal calibre with the re-expansion of a pulmonary collapse (Fig. 14a and b).

2. The peripheral end of the bronchus becomes

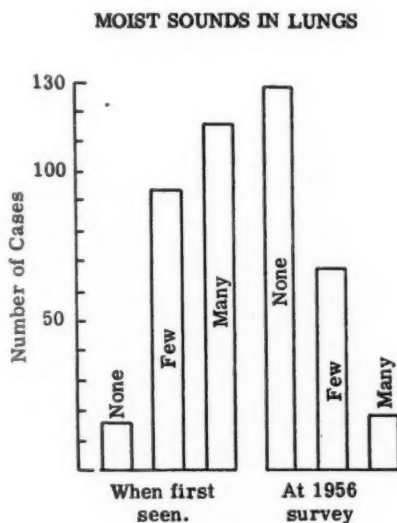


FIG. 13

TABLE 14

POSTURE IN PATIENTS SEEN IN 1956 SURVEY

Posture	Number of Patients	
	Medical	Surgical
Good .. ..	69	58
Slight defect .. ..	18	39
Bad .. ..	5	20
No record .. ..	12	4

TABLE 15

SHAPE OF CHEST IN PATIENTS SEEN IN 1956 SURVEY

Shape of Chest	Number of Patients	
	Medical	Surgical
Normal .. ..	67	54
Pigeon .. ..	10	13
Flattened .. ..	16	42
Spinal curve .. ..	6	16
No record .. ..	10	5

TABLE 16

CHEST EXPANSION IN PATIENTS SEEN IN 1956 SURVEY

Chest Expansion	Number of Patients	
	Medical	Surgical
Good .. ..	21	57
Average .. ..	55	48
Poor .. ..	11	10
No record .. ..	17	6

TABLE 17

DATA FOR FIG. 12

Clubbing	Number of Cases		
	When First Seen	1956 Survey	
		Medical	Surgical
Absent ..	145	86	101
Present ..	78	12	12
No record ..	2	6	8

TABLE 18

DATA FOR FIG. 13

Moist Sounds in Lungs	Number of Cases		
	When First Seen	1956 Survey	
		Medical	Surgical
None ..	16	55	74
Few ..	93	29	39
Many ..	116	15	4
No record ..	0	5	4

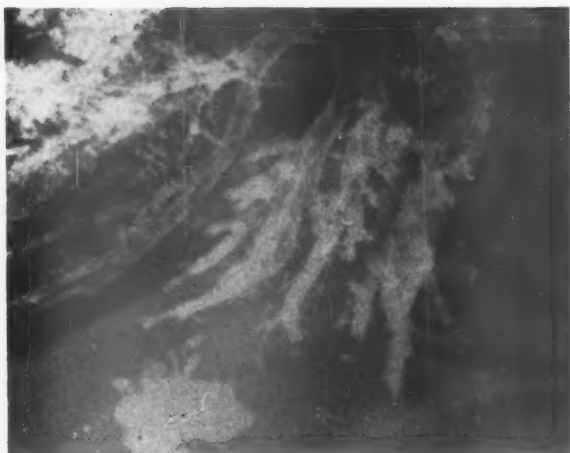


FIG. 14(a).—Left oblique bronchogram of a girl aged 7 years, showing the dilated lower lobe bronchi and the lingula lobe bronchi displaced downward and slightly dilated. The patient gave no history of cough only loss of weight and she easily became tired. Pulmonary collapse of the left lower lobe was revealed on a radiograph two months previously.

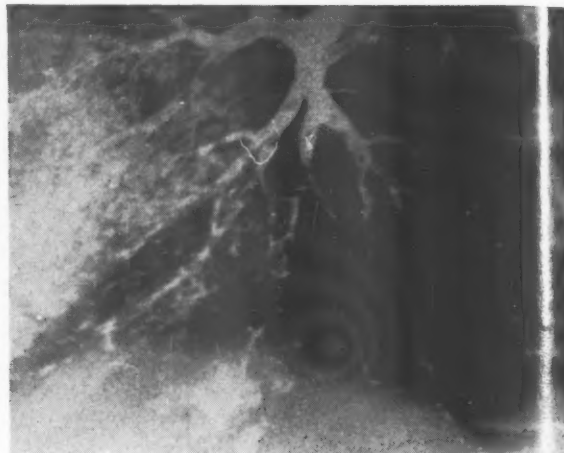


FIG. 14(b).—Left oblique bronchogram of the same patient repeated after one year and nine months. The dilated bronchi are now normal width.

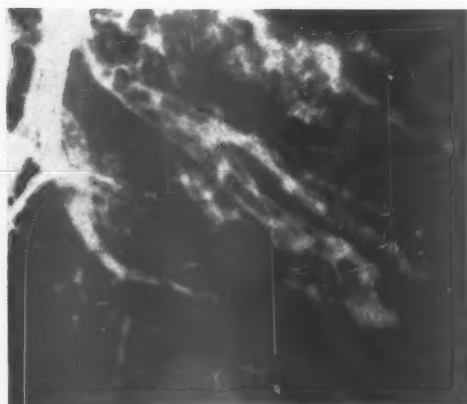


FIG. 15(a).—Right lateral bronchogram of a girl aged 4 years 9 months, showing the right middle lobe bronchi with tubular dilatation.

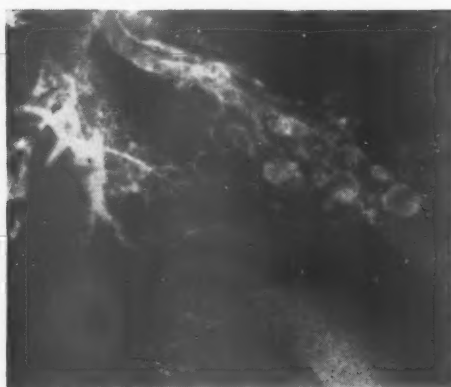


FIG. 15(b).—Two years later, showing cystic dilatation of the same bronchi as Fig. 15(a).

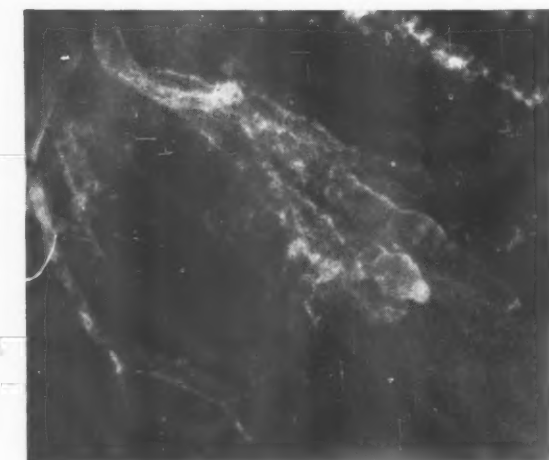


FIG. 15(c).—Repeat bronchogram after a further three years shows varicose dilatation of the middle lobe bronchi; the cystic areas are not filled but can be seen on the original film.

bulbous and often cystic (Fig. 15a and b). This is a sign of irreversible bronchiectasis.

3. The tubular dilatation takes on a varicose appearance (Fig. 15c).

In infants the tubular dilatation is often diffuse and difficult to define, but over the years it so commonly localizes itself to the dependent bronchi; in those bronchi in which gravity assists drainage the dilatation clears up. This accounts for the common occurrence of the distribution for bronchiectasis, i.e. the basal branches of the lower lobes, the right middle and lingula lobes and the antero-lateral branch of the upper lobes when the middle and lingula are affected. (When bronchiectatic,

the middle and lingular lobes take up a smaller space, displacing the antero-lateral branch of the upper lobes downwards.) The upper lobes and dorsal part of the lower lobes commonly escape. This shows the great importance of adequate drainage in the prevention and treatment of early bronchiectasis. After lobectomy of the middle and lower lobes, some of the upper lobe bronchi become dependant as the lobe re-expands to occupy a large space, and if these bronchi are in any way diseased they will become bronchiectatic. If the bronchi are healthy the lung expands well and the bronchi often appear to grow in length ultimately occupying a similar space to the whole lung before removal. This phenomenon is seen most strikingly in the younger child.

Bronchiectasis in association with tuberculous lesions develops slowly even when associated with tuberculous hilar glands. After many years it may still not be present if secondary infection has been prevented.

**Deaths.** Since the original publication (Field, 1949) when 19 deaths were reported out of 202 cases, 12 more patients have died. Seven of these had no operation. Only four died near enough to the 1956 survey to include in the clinical assessment. Table 19 gives an analysis of these deaths. Cases 1 and 2 were young children having had pulmonary resection some time previously, but whose general condition and pulmonary state progressively deteriorated; both patients were then suspected of suffering from fibrocystic disease of the pancreas, but this was never proved. Case 3 was observed from the onset when she developed cystic bronchiectasis after a virulent staphylococcal pneumonia which had been treated in the early days with sulphathiazole (Fig. 16a and b). Her condition was never satisfactory after this, and, in the final stages, her private practitioner found massive collapse of the left lung and extensive infection of the right. Case 4 was a child with an obscure myopathy, always frail and fragile. She died in hospital with a severe haemop-

TABLE 19  
ANALYSIS OF DEATHS

Case No.	Age at Death (years)	Sex	Extent of Bronchiectasis	Pulmonary Resection	Cause of Death	Autopsy
1	10	M	Bilateral, extensive	Right mid lobe and segmental right upper lobe Segmental right lower Segmental left lower	Suspected fibrocystic disease of pancreas not proved	No
2	10	F	Bilateral, extensive	Left lower lobe	Died in cardiac failure with cor pulmonale; also suspected fibrocystic disease of pancreas not proved	No
3	17	F	Bilateral, extensive after staphylococcal pneumonia	None	Left lung later collapsed and condition rapidly deteriorated; probably died of pneumonia	No
4	18	F	Bilateral, diffuse; also suffered from myopathy	None	Pneumonia; severe haemoptysis	No
5	19	F	Bilateral, diffuse with severe asthma	None	Died in cardiac failure with cor pulmonale; pulmonary oedema and bronchitis; lung abscess and generalized amyloidosis	Yes
6	20	M	Bilateral, diffuse with asthma	None	Died at home in cyanotic attack; radiograph showed cor pulmonale	No
7	21	M	Bilateral, diffuse with asthma	None	Doctor's report 'died at home with a story that sounded like cor pulmonale with ascites and oedema'	No
8	7	M	Bilateral, cystic	Left lower lobe Segmental right upper lobe	Died from oedema of lungs three days after second operation	Yes
9	11	F	Cystic right mid and lower lobes; scattered cysts in left lung	Right middle lobe	Died from toxæmia and renal failure 18 days after operation	No
10	6	F	Extensive	Left lower lobe	Died five years after operation with extensive bilateral cystic bronchiectasis	Yes
11	16	F	Cystic right upper lobe	None	Died in uraemia from chronic renal disease	No
12	23	M	Tubular right mid lobe and lingula	None	Died in motor cycle accident	No

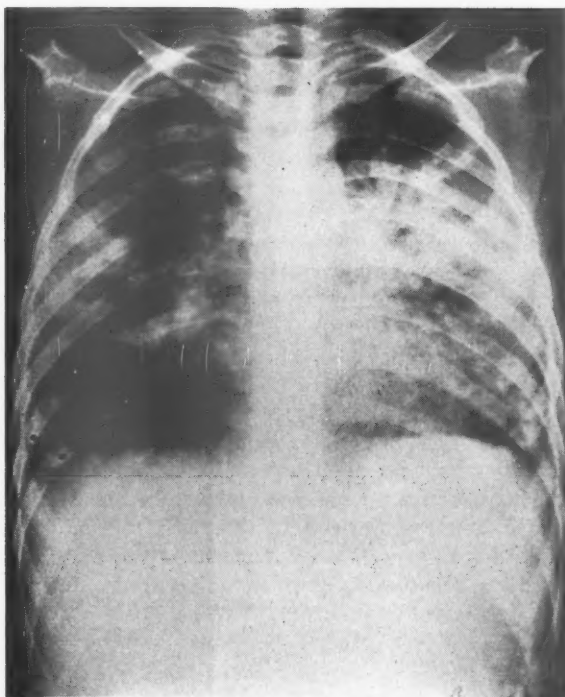


FIG. 16(a).—Antero-posterior radiograph of chest of a girl aged 10 years with staphylococcal pneumonia.

tysis after a recurrence of her chest infection. Cases 5, 6 and 7 suffered from extensive bilateral bronchiectasis with moderately severe asthma; the radiographs showed cor pulmonale and also marked emphysema. Cases 8 and 9 died in the early days of surgery. Case 10 was a patient with extensive bilateral cystic disease who died five years

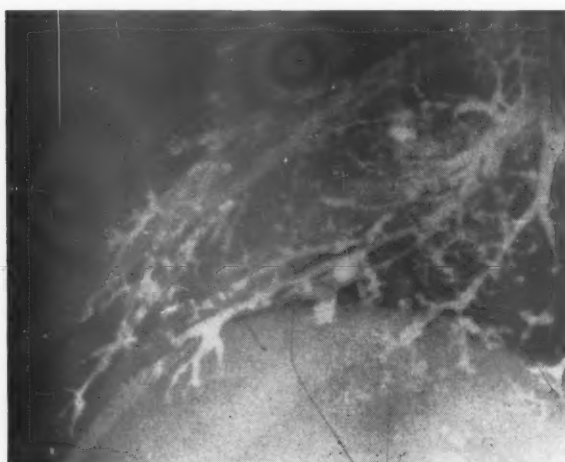


FIG. 16(b).—Left oblique bronchogram of the same patient three years later, showing part of the left lower and lingular bronchi with small cystic dilatations, which were present diffusely over both lung fields.

after removal of the left lower lobe. Cases 11 and 12 did not die as a result of their bronchiectasis.

It is the first three cases that are perhaps puzzling: the children whose bronchiectasis never seems to respond satisfactorily to treatment. There are a few of these cases still living, and, as can be seen, surgery does not help. The extent of the lung damage, the virulence of the infection, or an underlying general disorder such as fibrocystic disease of the pancreas or agammaglobulinaemia should be suspected.

### Discussion

In the past 10 years there have been several follow-up studies reported in the literature both for medically treated and surgically treated cases, and on the whole the results are favourable with the majority showing improvement and with some cases apparently clinically well (McKim, 1952; Strang, 1956; Dyggve and Gudbjerg, 1958; Franklin, 1958). The only study, however, that can be compared with the present series is that by Strang. He followed up 209 children all under 15 years at the time of onset of the disease; the duration of follow-up was shorter, two to 15 years. In 75% of his cases the onset of the disease was in the first five years of life; 51% showed clubbing and his cases may be, on the average, more severe than the series reported here. One hundred and sixty-three were treated surgically and 46 conservatively. There is no doubt that Strang was seeing the same trend of improvement and in fact the results in his surgically treated patients are very similar to those reported here. The prognosis in his medically treated patients is not quite so good, but this may be because, in the present series, 38 cases were mild cases, some of which were of doubtful permanency, and many of these are now symptomless and probably cured. Strang mentions the frequency of feverish chest illnesses which occurred in 130 of his 209 cases. It is these febrile attacks that can now be effectively controlled in most patients with antibiotics, thus changing to a certain extent the natural history of the disease.

Ogilvie, in 1941, records the results in 68 cases of bronchiectasis. Although these were followed for 'less than 6 years', nevertheless, they occurred in the era before the extensive use of antibiotics. Even in these cases 25 were well and symptom-free; 16 of these, however, were after operation. Fifteen had died, six after operation. Some of his cases, however, included adults as the average age was 17 years 3 months. Strang (1956) mentions a further follow-up for 11 to 18 years of 15 of Ogilvie's bronchiectatic children; five had died, two were

'cured', three had greatly improved and five remained the same but carried on a normal life.

McKim (1952) reviews 49 ambulant cases collected between 1930-41, which were followed up for nine to 20 years. The average age at the time of diagnosis was 31 years, so this series was, in the main, from a different age period. Nevertheless, he found that there was a general tendency to improvement, but that the longer the history of the disease the less good was the prognosis. Does this suggest that all cases of bronchiectasis improve for a time only or is it a question of the age factor?

Franklin (1958) divides his 20 patients into three categories: invalid, delicate, and absolutely well after the first assessment in 1944. In 1958 these patients had been followed for six to 22 years and their ages ranged from 15 to 34 years. The 11 patients who were absolutely well remained well; of the four delicate patients, two remained delicate and two became invalid, and of the five invalid patients, one had died, one had become well and the others had remained invalid or delicate. This second review suggests a slight overall deterioration, but on the whole there is not much change. Many of these patients are now in their twenties; only one is in the thirties.

In the series of cases reported here, there has been no classification of severity, largely because the review is essentially an overall review relating to the natural history of the disease process. Nevertheless, it is possible to study those patients who either died or whose condition has worsened. Strang (1956) states 'there was no evidence that the severity of the symptoms before operation had any bearing on the ultimate result'. With that I am inclined to agree as removal of a severe but localized cystic lobe can produce a symptomless patient. I have seen the same improvement occur in a severe case of bilateral sacular disease where operation was refused. The disease must have become 'dry' as, at the age of 16, the child had no cough or sputum and was stated to be well. Such a case, however, is a rarity; in general, those who are treated conservatively, may improve but continue to be severe. The mysterious cases are those who for no apparent reason deteriorate rapidly in spite of treatment by antibiotics. Case 3 (Table 19) was such a patient. Her fine diffuse cystic bronchiectasis following staphylococcal pneumonia did not look severe (Fig. 16a and b), yet her progress was never satisfactory; a superadded massive collapse of the left lung must have decided the ultimate outcome. It is probable that the disease in the lung was more extensive than the bronchograms suggested and that after the massive collapse she was left with inade-

quate pulmonary tissue for gaseous interchange. This is one of the most dangerous signs in cases of bronchiectasis usually manifesting itself with some degree of cyanosis. A further case illustrates this, a brother and sister were both affected with a somewhat diffuse type of bronchiectasis in childhood. The sister made good progress, but the brother never seemed well. Lobectomy was carried out and the most severely diseased parts were removed, but this produced little or no improvement; he has now reached the stage where he is unable to work due to fatigue and has cyanosis and breathlessness on exertion. The damage to the pulmonary alveoli in this patient is too extensive for satisfactory ventilation and in due course circulatory embarrassment will follow. These children have a bad prognosis, particularly as they reach adolescence and their physiological needs are greater. From Table 19 it can be seen that Cases 5, 6 and 7 are of this nature and probably Cases 1, 2, 3 and 4. Operative procedure on such cases is risky if the margin of healthy pulmonary tissue is small. Where progress is not satisfactory and the cause is doubtful, as in Cases 1, 2 and 3, it is advisable at first to culture the sputum for resistant organisms and then to test for systemic diseases such as fibrocystic disease of the pancreas (mucoviscidosis) or agammaglobulinaemia. Pittman (1960) tested 52 patients with established bronchiectasis for gammaglobulin concentration in the blood and found no deficiency, but she reports a case of bronchiectasis with severe hypogammaglobulinaemia. Other cases have been reported in the literature.

The prognosis in bronchiectatic cases with asthma is never good. Even if all bronchiectatic areas are removed, the symptoms persist. Strang (1956) states 'the presence of asthmatic symptoms before operation does seem to influence the result'. In patients treated conservatively it may add to the pulmonary strain thus producing emphysema, pulmonary hypertension and cardiac failure as in Cases 5, 6 and 7 (Table 19).

In the present series there were 38 cases in the medically treated group in which it was impossible to say whether the tubular dilatation was likely to be permanent. In a few it was permanent as proved by repeat bronchography and some of these have been subjected to lobectomy; in others the symptoms have persisted, suggesting a permanent lesion, but in many all symptoms and signs have disappeared, and it is possible that in some of these the tubular dilatation has reverted to normal (Fig. 14a and b). This reversible phenomenon in children is important to remember, otherwise unnecessary lobectomy

may be performed. Williams and O'Reilly (1959) describe two pathological types of bronchiectasis: (a) that with subacute pyogenic pulmonary collapse and (b) that with non-specific infective bronchiolitis and/or interstitial pneumonia. They believe that with chemotherapy, postural coughing and physiotherapy many cases of type (a) will show complete or partial resolution of collapse and bronchiectasis, but that such treatment is less effective in type (b). It is therefore important to recognize those cases which may still be considered reversible (see later).

Surgery for bronchiectasis must of necessity be selective, but practice has changed over the years from the removal of grossly diseased lobes or lungs only, to segmental resection in an attempt to remove all diseased parts and at the present day to the more conservative surgery of removing only grossly diseased parts or definite localized bronchiectasis. The present series of cases fell largely into the middle group and many patients underwent several operations for partial resection. If patients treated medically and those treated surgically can be compared, it is that more surgically treated patients have improved whereas more medically treated patients have remained the same (Fig. 5); in Strang's series (1956) this was the case. However, if surgical selection is correct the patient ought to improve. Nevertheless, many surgically treated patients can become symptomless even when some residual bronchiectasis persists. Rosemond, Burnett and Humphrey-Long (1951) report on the follow-up of 159 surgically treated patients. In 55 patients there was residual disease yet 14 of these were symptomless. Nevertheless, the reverse phenomenon is not uncommon where post-operative bronchograms show no bronchiectasis yet the child remains with a persistent cough and symptoms. Strang (1956) remarks on this and suggests that it might be caused by sinusitis or a generalized bronchitis. If Williams and O'Reilly (1959) are correct in their pathological differentiation then type (b) (see above) in which there is a non-specific infective bronchiolitis and/or interstitial pneumonia will lead to a more generalized disease with persistent symptoms after the bronchiectatic lesions have been removed. Allergy may also be the cause in some patients.

In the selection of cases for surgery therefore, many important points must be considered and each patient is an individual problem. The following points may be of value:

(1) Grossly diseased parts, particularly if saccular, are better removed provided that enough healthy lung can be left.

(2) Moderately severe dilated bronchi with

symptoms, if localized, are probably best removed.

(3) Cylindrical bronchiectasis with a bulbous or saccular periphery (Fig. 15b) where symptoms are troublesome is probably best removed, if it is localized, as this type is irreversible.

(4) Cylindrical bronchiectasis in children should be left alone and watched even if it is associated with symptoms. Some of it will be reversible, and some will revert to the fusiform or varicose types with a good prognosis.

(5) Diffuse bronchiectasis should be left alone unless a grossly diseased localized area is also present (see (a) above).

(6) If the child has asthmatic symptoms the prognosis is less promising. These patients tend to remain with their asthmatic symptoms or chronic bronchitis.

Does bronchiectasis spread? This is not easy to answer because superadded pneumonic processes or pulmonary collapse may themselves cause a spread of the disease. However, in the severe type of bronchiectasis with much sputum it is possible for adjacent dependent bronchi to be subject to tip over secretions with mild bronchiectasis. Furthermore, if the remaining lung is not completely healthy after lobectomy, the bronchi which become dependent may develop bronchiectasis or, if already dilated, may become more dilated. On the whole, bronchiectasis is not a spreading disease and usually remains confined to the lobes originally affected. Strang (1956) states 'there was no evidence from a study of these cases to support this concept of bronchiectasis as a spreading process'. But Dyggve and Gudbjerg (1958) found new dilatation in three out of 11 post-operative cases.

In the series of cases reported here no special study has been made of the part played by antibiotics in the natural history of the disease, but it is known that most (if not all) patients received antibiotics for the febrile respiratory infections from time to time. Comparison of cases occurring before the use of antibiotics and those of the present day is of little value as diagnosis of milder cases is made more frequently today, thus making the two groups incomparable. Furthermore, the old concept of the disease as a crippling disorder with a high mortality may have been related mainly to the severe types diagnosed by clubbing and fetid sputum. With the modern facilities of chemotherapy, surgery and postural drainage with physiotherapy, the history of bronchiectasis from childhood is one of considerable improvement particularly around puberty in the second decade. Whether this improvement will be maintained in adult life remains to be seen.

### Summary

A clinical review of 225 cases of bronchiectasis is given; 104 of these were treated medically and 121 surgically. The patients have been followed for eight to 21 years at the time of report and their ages range from 10 to 29 years. There is a slight preponderance of females.

In 169 patients the onset of the disease was in the first five years of life; thereafter there was some improvement which became most marked in the second decade around puberty. In the twenties the condition seems to be stationary. The results were slightly better in the surgically treated patient, but the two groups are not comparable.

Of the patients, 53% have suffered from an intercurrent respiratory infection or asthma during the past six years and some have frequent attacks. None complained that the disease affected their marriage, but in one patient it created a complication.

There was no cough in 33% and in 44% no sputum. Nasal discharge, although less troublesome to some, still persisted in others and was a possible cause of cough. Wheezing at times was complained of by 42%, and undue breathlessness on exercise by 53%. This was more marked in the surgically treated patients.

Postural defects and abnormal shape of the chest were not uncommon features particularly in the surgically treated patients. A surprise finding was in the growth records for height and weight. There was a tendency for the records to be under the 50 percentile and a few patients were grossly underweight, particularly the medically treated patients.

Clubbing had disappeared in about 69% of the patients in whom it was originally reported. In 57% of the patients no moist sounds could be heard in the lungs even in patients with habitual cough.

Twelve deaths are reported since the original published records (Field, 1949): five surgically treated, five medically treated and two patients who died from causes other than the chest. All the patients except the last two were suffering from extensive bilateral disease.

It appears from the above records that the history of bronchiectasis between 1938 and 1956 in this series of cases shows an early onset mainly in the first five years of life, a gradual improvement, particularly around puberty, but with troublesome intercurrent chest infections which seemed to be well controlled with chemotherapy and antibiotics. Mortality after infancy was confined to patients with bilateral extensive disease.

I am greatly indebted to members of the Research Committee of The Hospital for Sick Children, Great Ormond Street, for allowing me to continue this follow-up study and for arranging all the necessary facilities. I am also very grateful to Professor R. S. Pilcher of University College Hospital, London, and his staff who so kindly collected the data on the surgical cases, the majority of which are being followed regularly by them, and also to Professor Pilcher for his continued advice and assistance.

I would also like to thank the staff of The Hospital for Sick Children, Great Ormond Street, and the Paediatric Department, University College Hospital, for their assistance in this follow-up study. In particular I am greatly indebted to Mr. J. B. Ready, Medical Records Officer, for his co-operation and help. Finally, I would like to thank Mr. D. Martin and the staff of the Department of Medical Illustration for the photography and charts.

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# SERUM ENZYME ACTIVITY IN THE NORMAL NEWBORN INFANT

BY

J. KING and M. BRENDA MORRIS

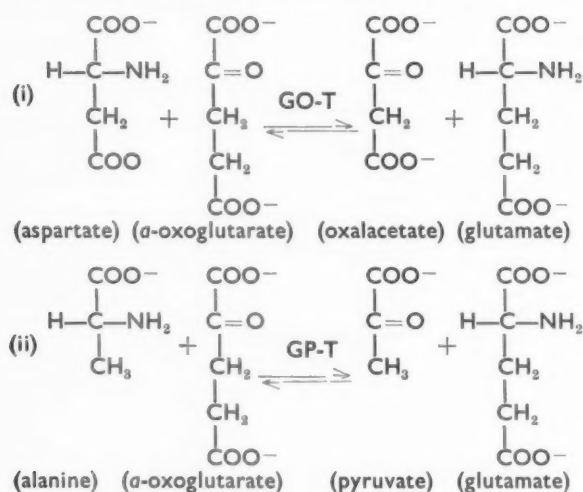
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The assay of serum enzymes has been used increasingly in recent years as an aid to clinical diagnosis and prognosis, but the literature contains few references to the exploitation of these laboratory tests in paediatrics.

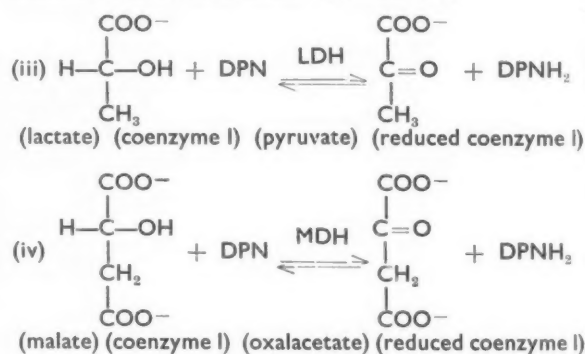
Following the development in these laboratories of assay procedures for glutamate-oxalacetate transaminase (GO-T), glutamate-pyruvate transaminase (GP-T), lactate dehydrogenase (LDH) and malate dehydrogenase (MDH) suited to routine work, the determination of the normal serum activities of these enzymes in the neonatal period was undertaken in conjunction with an investigation of the usefulness of their estimation in haemolytic disease of the newborn.

The transaminase enzymes form a link between protein and carbohydrate metabolism and mediate in the reactions shown in equations (i) and (ii).



Lactate dehydrogenase is a glycolytic enzyme and malate dehydrogenase catalyses the final step in the tricarboxylic acid cycle. These biocatalysts, as found in human blood serum, require coenzyme I

(diphosphopyridine nucleotide—DPN) as hydrogen carrier and exhibit greatest activity in the reactions summarized by equations (iii) and (iv).



## Methods and Materials

Glutamate-oxalacetate transaminase (GO-T) and glutamate-pyruvate transaminase (GP-T) activities were estimated by the methods of King (1960a). As the colorimetric procedures for the assay of serum lactate dehydrogenase (King, 1959, 1960b) and malate dehydrogenase (King, 1961) are rapid and require small quantities of serum they were found to be suited to the present survey.

Bilirubin levels were determined by a micro adaptation of the method of Malloy and Evelyn (1937), checked on numerous occasions when the sample permitted by the spectrophotometric technique of Scott (1959). Good agreement was obtained between the two methods. The latter procedure was found to give an indication of degree of haemolysis which in icteric serum is sometimes difficult to decide by inspection.

The material consisted of 154 cord bloods and 41 specimens of blood taken from normal full-term infants on one occasion during the first nine days of life. Since GO-T and GP-T activities for whole blood are approximately five and three times respectively those of serum, while for LDH and MDH the ratio ranges from 100 to 150, specimens showing any visible haemolysis were discarded for purposes of dehydrogenase assay and only the slightest haemolysis was tolerated for the determination of transaminase activity.

TABLE 1  
NORMAL CORD BLOOD VALUES

	Mean	Standard Deviation	98% Observed Values	Adult Range
Bilirubin (mg./100 ml.)	1.86	$\pm 0.51$	0.6-3.4	<1.0
GO-T (International units)	15.1	$\pm 4.1$	6-25	6-18
GP-T (International units)	5.5	$\pm 2.5$	1.3-11	3.5-15.5
LDH (International units)	330	$\pm 82$	150-590	70-230
MDH (International units)	52.5	$\pm 13$	22.5-98	10-44

Cord blood was obtained by letting the blood drip from the maternal end of the cut cord into the collecting bottle, and the subsequent specimens from the babies were obtained by puncture of a scalp vein.

All babies in the normal series were full-term babies of birth weight over 5 lb. 8 oz. In the case of the 154 babies whose cord bloods were taken, there was no abnormal jaundice in the neonatal period, and in the case of the 41 babies whose blood was taken at some time in the first nine days of life, every baby was personally observed by one of us (M.B.M.) throughout the first 10 days of life, and their course during this time was normal.

In all cases both mothers' and infants' blood groups were determined and in the 41 infants from whom a second blood specimen was obtained the direct Coombs test was negative.

### Results

**Cord Blood.** The statistical analysis of figures for the normal cord blood serum is presented in Table 1, together with normal adult values obtained using the same methods. The units originally used in this work were those defined by Antebi and King (1958), but recently an international enzyme sub-commission has recommended the use of an International Unit (King and Campbell, 1961) for expressing serum enzyme activity and the results obtained in the present study are recorded in International Units. This unit is that which will transform  $1\mu$  mole of substrate per minute under the prescribed assay conditions, activity to be expressed per litre.

Similar to the figures obtained in adults, the distributions of all these cord blood enzyme activities are found to be of the 'log normal' type (Gaddum, 1945) and positively skewed. A normal range in terms of mean and standard deviation cannot be expressed under these circumstances and following the arguments of Wootton and King (1953) the range is best expressed by upper and lower 1% limits which enclose 98% of the distribution. Figures falling outside these limits may be regarded as abnormal.

It is seen that for GO-T, LDH and MDH the range of values encountered is wider and higher by

a factor 1.5 to 2.5 than the respective figures found in normal adults. GP-T on the contrary was found to have a narrower and lower range. MDH was found to parallel LDH so closely, the ratio of activities approximating to 1 : 6, that it is not proposed to treat it separately.

Figs. 1 to 3 are scattergrams showing the relation

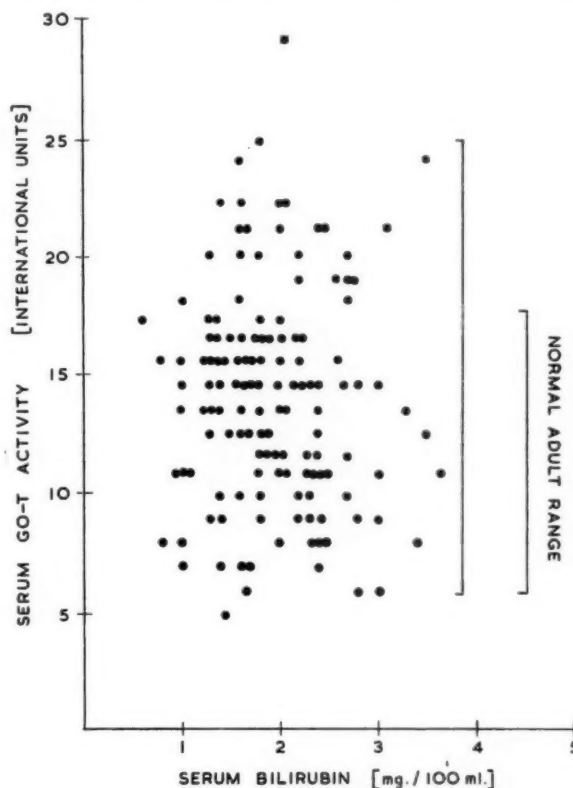


FIG. 1.—Variation of cord GO-T activity with bilirubin.

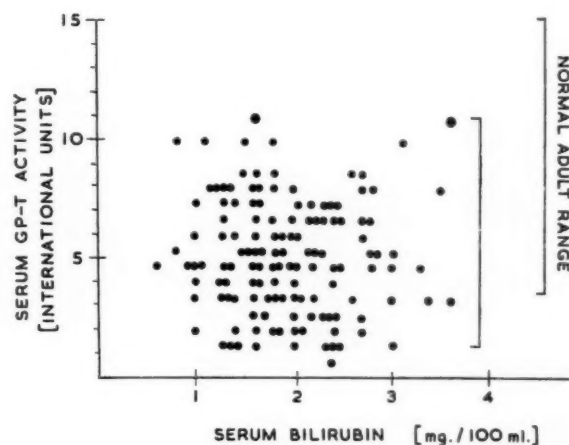


FIG. 2.—Variation of cord GP-T activity with bilirubin.

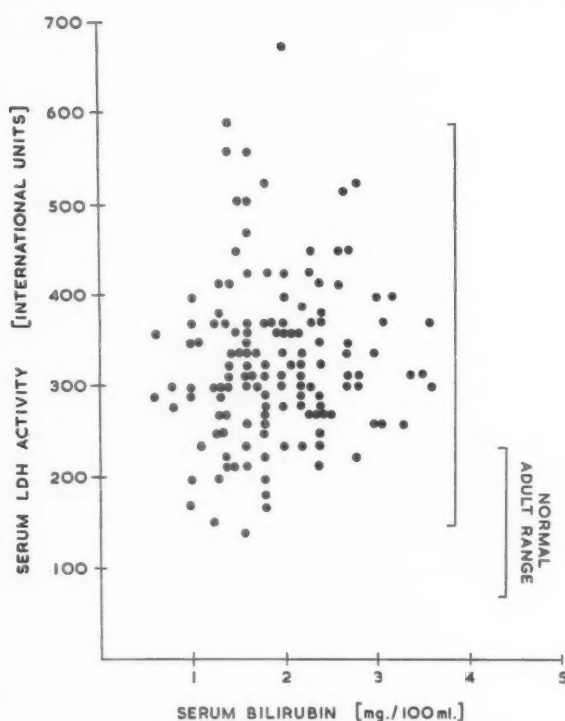


FIG. 3.—Variation of cord LDH activity with bilirubin.

between serum enzyme activity and bilirubin levels. These show, not unexpectedly, that there is no correlation between serum bilirubin and any of these enzymes.

No correlation between any of the five biochemical parameters studied, with the exception of LDH and MDH, was found, and no significant difference with sex of the infant could be demonstrated.

The values for normal cord blood GO-T and GP-T activities, together with cord blood figures obtained in some premature infants are shown in Figs. 4 and 5 plotted against gestation period irrespective of birth weight. LDH and MDH patterns were similar to that for GO-T inasmuch as all values fell within the normal cord blood range with no obvious change in distribution. GP-T activity, however, did appear to show some decrease with premature delivery, but the number of the sample is too small to demonstrate any significant change.

**Normal Newborn Infants.** The results obtained from enzyme assays of the 41 'second' specimens, together with the respective cord blood figures are summarized in Figs. 6 to 8 where enzyme activity is plotted against day of life. For GO-T and LDH

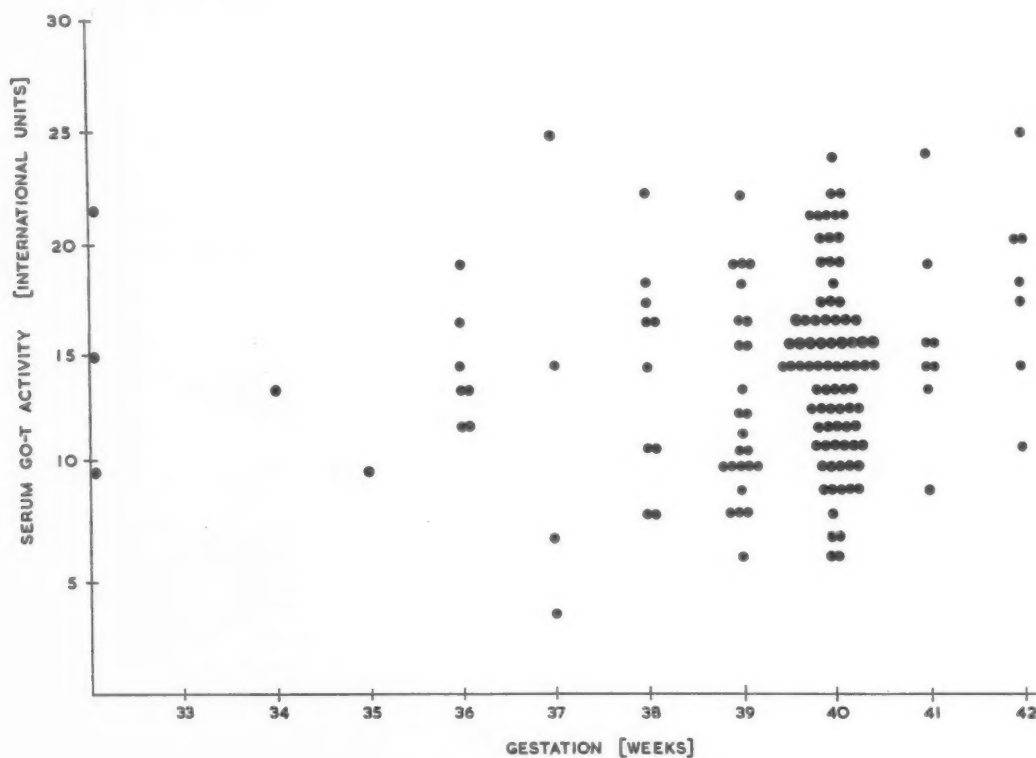


FIG. 4.—Variation of cord GO-T activity with gestation.

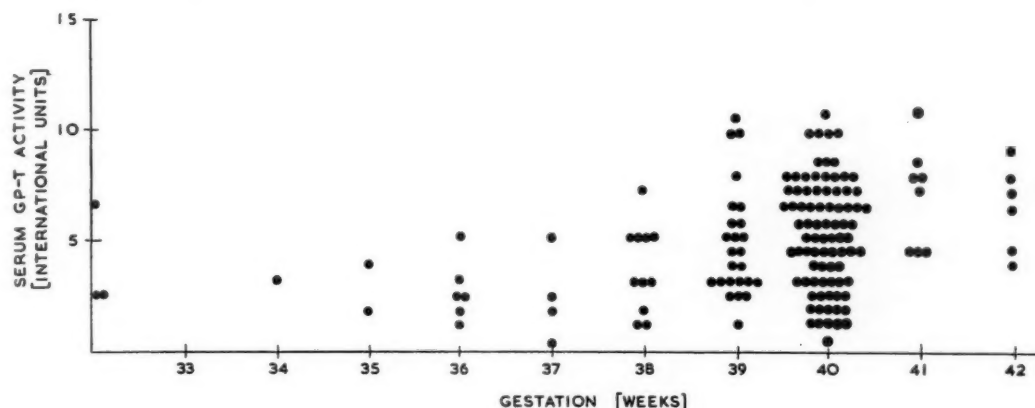


FIG. 5.—Variation of cord GP-T activity with gestation.

and, hence MDH, no variation of enzyme activity was noted either with day of life or with bilirubin level. All figures fell within the range of normal cord blood activity without any obvious significant change in distribution, although the number of the sample is too small for statistical analysis.

Despite this mathematical limitation, however,

the increase in GP-T activity with age particularly after the seventh day of life cannot be ignored.

The serum bilirubin figures at this age were found, as expected, to have fallen to low levels, and plotting GP-T activity against bilirubin tends to indicate that there is an inverse proportionality between the two entities, which would be misleading. It is an

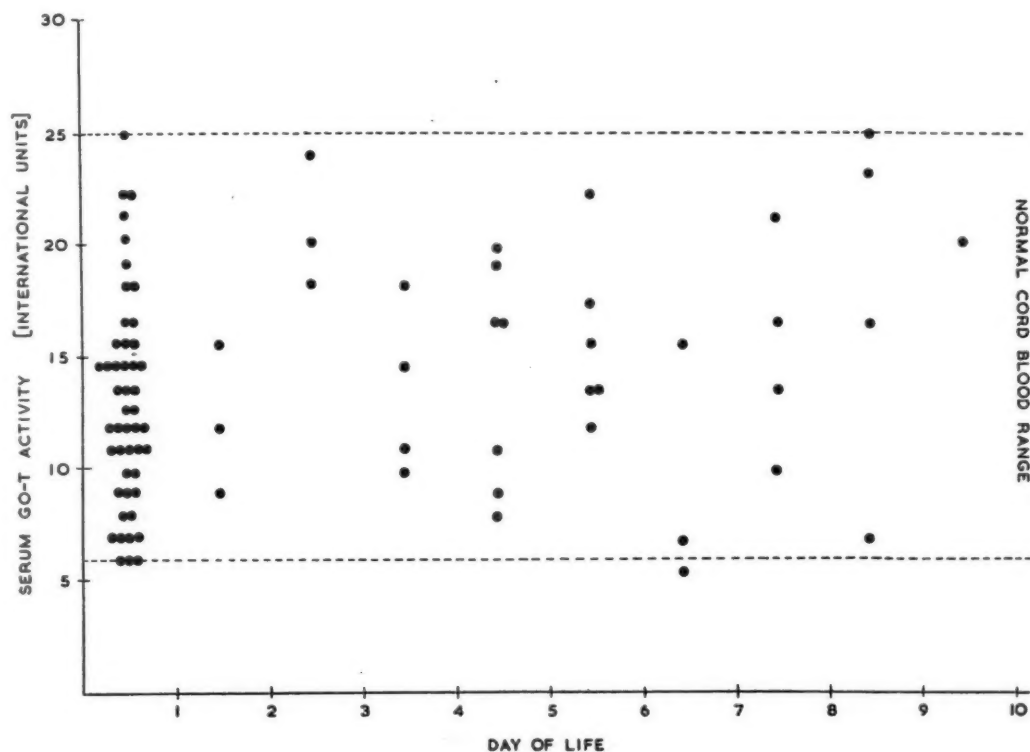


FIG. 6.—Variation of GO-T activity with age.

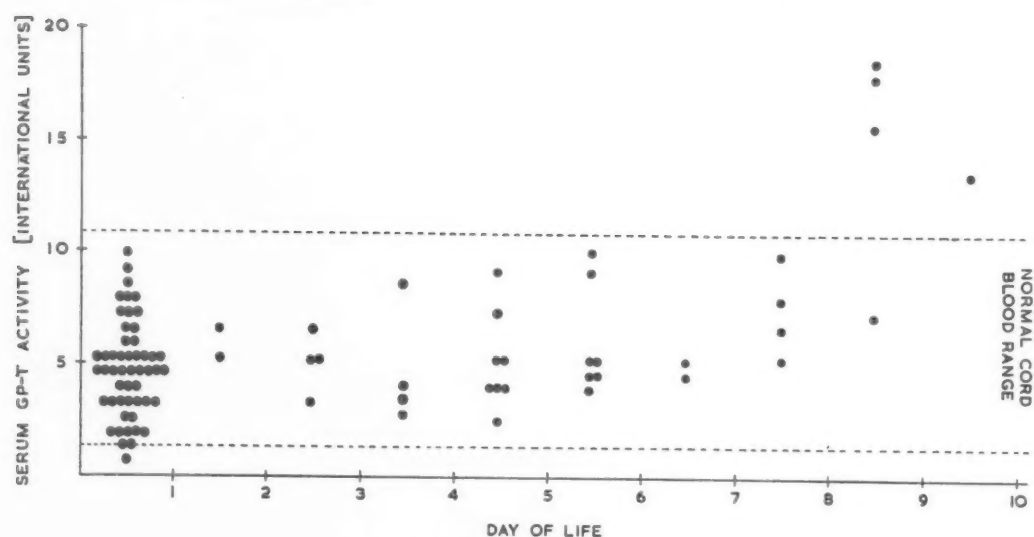


FIG. 7.—Variation of GP-T activity with age.

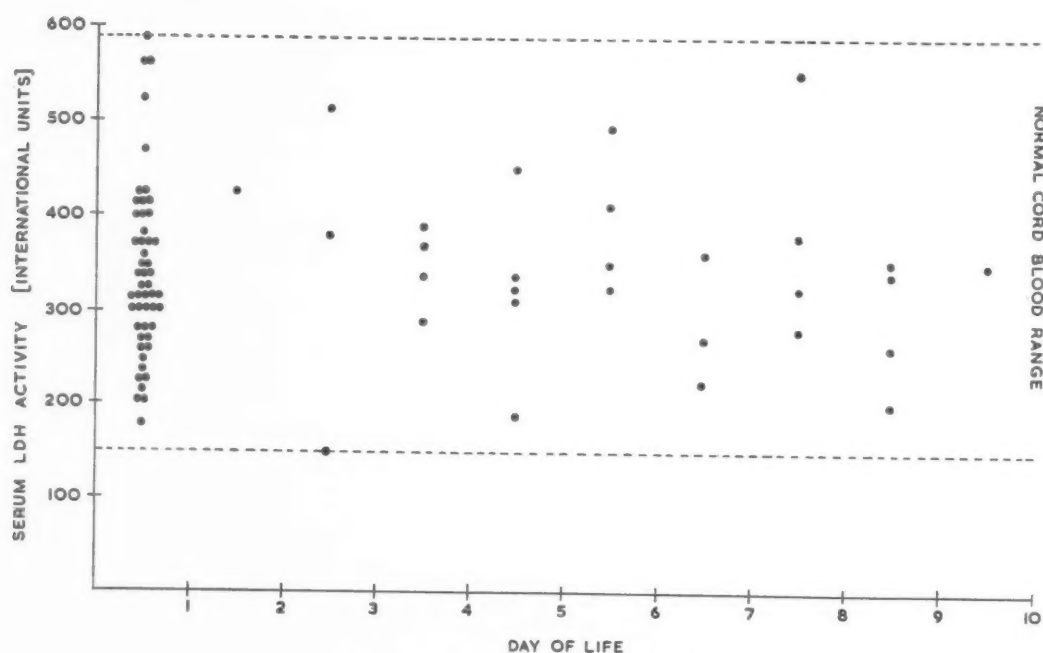


FIG. 8.—Variation of LDH activity with age.

attractive speculation, however, to connect the known decrease in bilirubin levels after the fifth day of life with the increasing activity of GP-T in the serum.

#### Discussion

Kove, Goldstein and Wróblewski (1957a, 1957b) assayed GO-T and GP-T from nine normal cord

bloods and found values of 20 to 59 units (Karmen, 1955) and 12 to 40 units respectively. The adult values by this method were given as 5 to 45 units for GO-T and 5 to 40 units for GP-T, but were later (Kove, Perry and Wróblewski, 1960) modified to 8 to 40 units and 5 to 35 units respectively. A conversion factor of approximately 0.45 transforms Karmen units to those used in this survey,

whence it will be seen that there is reasonably good agreement for cord GO-T figures.

The values found in the present study for GP-T, however, are lower and the range narrower than those accepted by these workers despite the small number of their sample.

In a further 54 infants aged from 1 to 11 days, values for GO-T from 13 to 105 units (with one of 160 units which was discounted) were encountered, and for GP-T figures from 8 to 80 units were obtained with a peak activity in the fourth to fifth day of life (Kove *et al.*, 1957a and b). These workers included in their normal series five out of nine babies with cord serum bilirubin values over 3 mg./100 ml. Higher values may occur in normal babies, but only rarely (Hsia, Allen, Diamond and Gellis, 1953). In their series also there were three babies with serum bilirubin values of 18 mg., 33 mg. and 17.5 mg. on the second, third and fourth days respectively. It is very unusual to obtain values higher than 15 mg./100 ml. in normal babies. Hsia *et al.* (1953) found no value above 14 mg./100 ml., and in our normal series we had only one value above 14 mg./100 ml., i.e. one sustained level of 17-18 mg./100 ml. from the fifth to the tenth day for which we found no cause. While these high levels do occur for no discoverable reason, they seem to be so rare as to suggest that they must, nevertheless, be pathological. Kove *et al.* (1957a and b) do not appear to have excluded haemolytic disease due to ABO incompatibility in their group of babies. The data for GO-T and GP-T presented in this paper are in disagreement with these earlier figures.

Using the same assay procedure, Stanton and Joos (1959) found lower values ranging from 29 to 72 units in 15 infants from 2 to 6 days of age, and West and Zimmerman (1958) found GO-T activity to be elevated above the upper adult limit of 40 units in four out of 19 cord bloods. The values of these sera were 48, 50, 113 and 114 units. LDH activity assayed on the same 19 sera was found to be twice the adult normal levels with very slight overlap of ranges. Hill (1956) has previously reported higher levels of LDH activity in normal children which approached the adult range at about 14 years of age. Lending, Slobody, Stone, Hosbach and Mestern (1959) in 54 infants from 2½ to 10 days of age found LDH activity to be elevated to three times the normal adult level. The present survey agrees with these earlier findings for LDH.

A search of the literature reveals no previous report of MDH activity in the neonatal period.

### Summary

A study of the activity of the enzymes, glutamate-oxalacetate transaminase (GO-T), glutamate-pyruvate transaminase (GP-T), lactate dehydrogenase (LDH) and malate dehydrogenase (MDH) has been carried out on 154 normal cord bloods and on 41 bloods from infants during the first nine days of life. A range of normal values for these enzymes is proposed.

The brief literature on the subject is reviewed.

We are indebted to Dr. J. E. Horrocks and Dr. J. Ward for much helpful advice and criticism and to Mrs. Mary Robinson for secretarial work. Our grateful thanks are also due to the house surgeons and nursing staff at Risedale Maternity Hospital and the technical staff of the Group Pathology Laboratory, without whose willing co-operation this work could not have been undertaken.

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# SERUM ENZYME ACTIVITY IN PREMATUREITY AND IN HAEMOLYTIC DISEASE OF THE NEWBORN

BY

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In a concurrent study of the serum activity of glutamate-oxalacetate transaminase (GO-T), glutamate-pyruvate transaminase (GP-T), lactate dehydrogenase (LDH) and malate dehydrogenase (MDH) in normal newborn infants ranges of normal values for these enzymes have been defined (King and Morris, 1961). In the present report the activity of these enzymes in relation to neonatal jaundice and in prematurity and haemolytic disease due to rhesus and ABO incompatibility is investigated. This work was undertaken in an attempt to elucidate the factors in the different types of jaundice and to see what help these estimations might afford in the practical management of exchange transfusion.

## Methods and Material

The biochemical techniques used in this study were those employed in the establishment of normal values for the neonatal period and reported elsewhere.

Except in very occasional cases the blood samples were obtained by scalp venepuncture.

**Prematurity.** Twenty-one babies defined by a birth weight of 5 lb. 8 oz. or under, irrespective of gestation period, had one or more enzyme estimations during the first week of life, and of these, seven also had enzyme estimations on the cord blood.

Sixteen babies had more than one estimation of any one enzyme, excluding cord blood values, and nine babies each had one exchange transfusion for hyperbilirubinaemia. The criterion for performing enzyme estimations was the clinical necessity for bilirubin estimation as suggested by an icterometer reading of 3 (Gosset, 1960). There are thus no premature babies in this group whose bilirubin levels remained low, excluding cord blood values.

**Haemolytic Disease of the Newborn.** (a) Anti-Rh: nine babies of which all had one or more exchange transfusions. Eight of the nine babies had three or more estimations of one or more enzymes. (b) Anti-A: 12 babies including one set of twins of which five had one or more exchange transfusions. Ten of these babies had three or more estimations of one or more enzymes.

The criteria for the diagnosis of haemolytic disease anti-A were as follows:

(i) Appearance of clinical jaundice within 24 hours of birth.

(ii) Mother found to be blood group O, and baby blood group A.

(iii) Negative Coombs' test on baby's blood. (This was done in most, but not all, cases.)

(iv) Demonstration of immune anti-A in the mother's blood by a qualitative test for haemolysins (Dunsford and Bowley, 1955) in all cases.

It is notoriously difficult to make a firm diagnosis of haemolytic disease of the newborn due to ABO incompatibility, but the presence of clinical jaundice in the first 24 hours of life and with subsequent high bilirubin levels, together with the serological tests performed, seem adequate to make this diagnosis probable.

## Results

In all three groups, we found differences in the GO-T and GP-T values compared with the normal for this age group (King and Morris, 1961). In all groups the findings are described in two parts: first, findings before exchange transfusion and where there was no transfusion, and including cord blood values, and second, findings after exchange transfusion.

### (1) Before Exchange Transfusion, or where there was no Transfusion

**Premature Babies.** GO-T in 50 estimations: 10 were between 25 and 33 I.U.; eight were over 33 I.U. (normal range 6-25 I.U.). GP-T in 45 estimations: Five were above 11 I.U. (normal range 1.3-11 I.U.).

**Haemolytic Disease Anti-Rh.** Pre-transfusion figures only are given. In this group it must be remembered that all cases were exchange-transfused within the first 24 hours of birth.

GO-T in 14 estimations: Two were between 25 and 33 I.U.; four were over 33 I.U. GP-T in 15 estimations: Three were above 11 I.U.

**Haemolytic Disease Anti-A.** GO-T in 27 estimations: Four were between 25 and 33 I.U.; 13 were above 33 I.U. GP-T in 27 estimations: 10 were above 11 I.U.

These points are illustrated in Figs. 1 and 2.

Table 1 is compiled from those cases in which there were three or more estimations of any one enzyme in the same baby, and illustrates the same point.

These figures demonstrate that there is an abnormality of serum enzyme activity in these three groups as compared with normal babies of the same age, and that this abnormality is only present in a very small proportion of the premature babies, but occurs in a higher proportion of babies affected by haemolytic disease of the newborn anti-Rh, and in an even higher proportion of those suffering haemolytic disease of the newborn anti-A.

(2) **After Exchange Transfusion.** Here it is seen that the abnormality of enzyme values is more pronounced, and that this occurs in an even higher proportion of the babies suffering from haemolytic disease anti-A.

TABLE 1  
FINDINGS IN CASES NOT TRANSFUSED AND BEFORE FIRST TRANSFUSION

	Pre-matures	Rh	ABO		Pre-matures	Rh	ABO
GO-T 25-33	6			GO-T <33	11	5	5
GO-T >33	5	3	5	GP-T <11	14	6	2
GP-T >11	2	2	8	GO-T <33 GP-T <11	8	5	1
GO-T >33 GP-T >11	1	2	4	LDH <590	12	4	10
LDH >590	none	2	2				

Figures represent numbers of babies in which one or more of the respective enzyme values is abnormal.

Figures represent numbers of babies in which all enzyme values are normal.

16 Prematures, eight haemolytic disease anti-Rh, 10 haemolytic disease anti-A.

Table 2 gives the figures obtained in all the babies after exchange transfusion. The figures represent the number of transfusions following which the respective values were obtained. This is in contrast to Table 1 in which the figures represent cases.

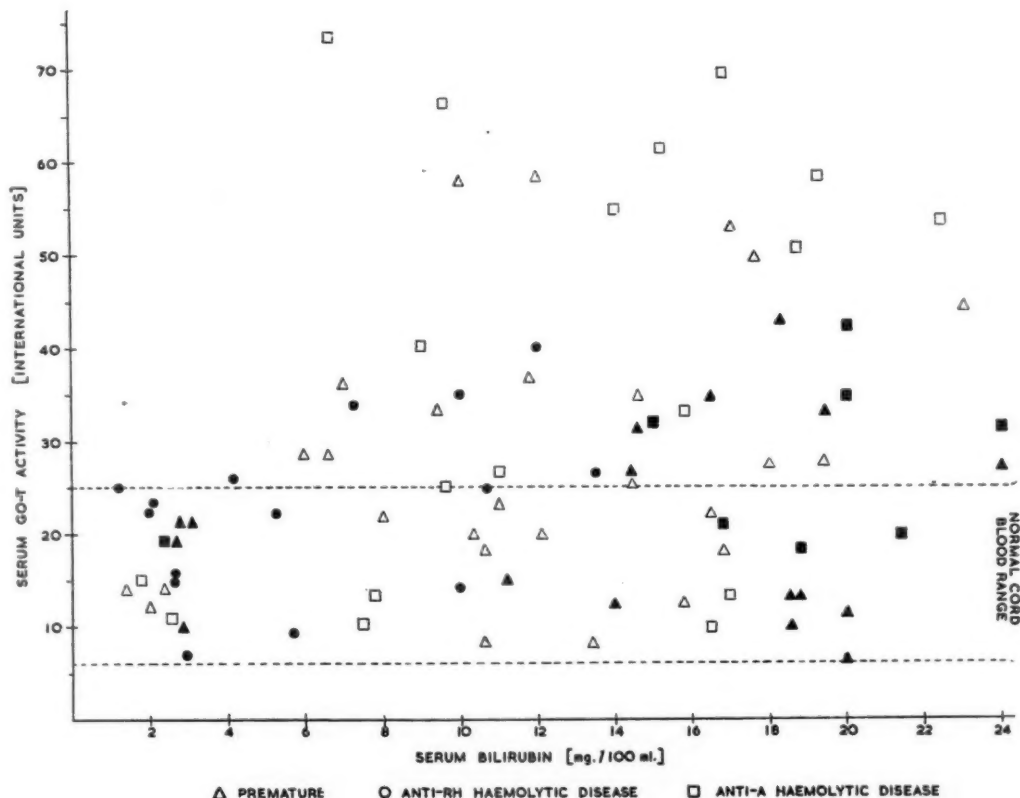


Fig. 1.—Serum GO-T activity and bilirubin in prematurity and haemolytic disease. Blackened symbols indicate infants transfused later.

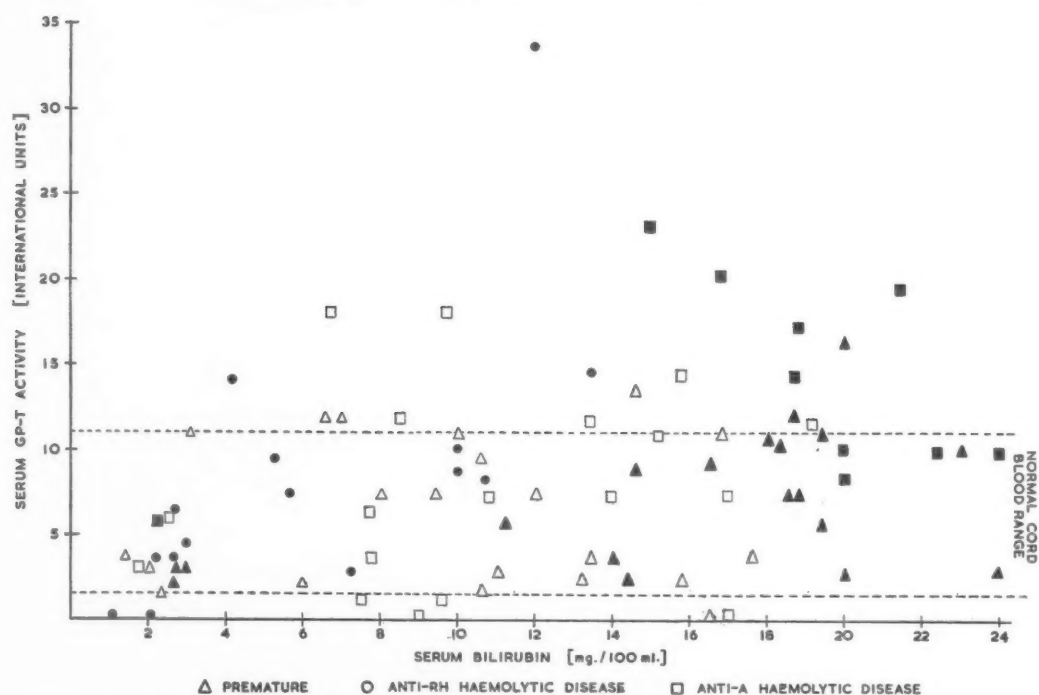


FIG. 2.—Serum GP-T activity and bilirubin in prematurity and haemolytic disease. Blackened symbols indicate infants transfused later.

### Discussion

Serum values for GO-T and GP-T are known to be raised in liver disease. GP-T is more sensitive than GO-T in indicating acute hepatocellular damage (Wróblewski and LaDue, 1956). It is a well-known clinical observation that in haemolytic disease the degree of jaundice does not parallel the degree of haemolysis, and is accentuated in those babies that are born prematurely. The lack of correlation between the degree of haemolysis and the degree of jaundice is striking in haemolytic disease anti-A

where jaundice can be very severe and where haemolysis is usually minimal. This phenomenon is considered to be related to the function of the liver, and these figures seem to support this view. It is not known, however, why the liver function is not satisfactory. Clinically this is not due to prematurity, although it may be accentuated by it. Again, these figures seem to illustrate this point.

The post-transfusion figures suggest that the liver dysfunction is in some cases accentuated by the transfusion. We had considerable difficulty with some of our cases whose bilirubin levels continued to rise even after transfusion of 80 ml./lb. body weight of blood, and we felt that we were not achieving a good result. This is demonstrated by the enzyme figures.

Graphs of individual babies in each group illustrate the points. Fig. 4 demonstrates the findings in a typical premature baby having an exchange transfusion, and here there were no abnormal enzyme values. Fig. 5 illustrates the findings in a case of haemolytic disease anti-Rh who had three exchange transfusions and here there are abnormal values. The washing-out effect of the transfusion is well shown. Figs. 6 and 7 illustrate findings in two cases of haemolytic disease anti-A in which exchange transfusions were carried out. Abnormal pre- and post-transfusion enzyme values are shown,

TABLE 2  
FINDINGS AFTER TRANSFUSION

	Pre-matures	Rh	ABO		Pre-matures	Rh	ABO
GO-T > 33	1	4	8	GO-T < 33	8	10	1
GP-T > 11	3	5	9	GP-T < 11	6	10	none
GO-T > 33	1	4	8	GO-T < 33	5	9	none
GP-T > 11				GP-T < 11			
LDH > 590	1	3	4	LDH < 590	5	8	5

Figures represent numbers of transfusions following which one or more enzyme values is abnormal.

Figures represent number of transfusions following which all enzyme values are normal.

Nine prematures, nine transfusions; eight haemolytic disease anti-Rh, 16 transfusions; five haemolytic disease anti-A, nine transfusions.

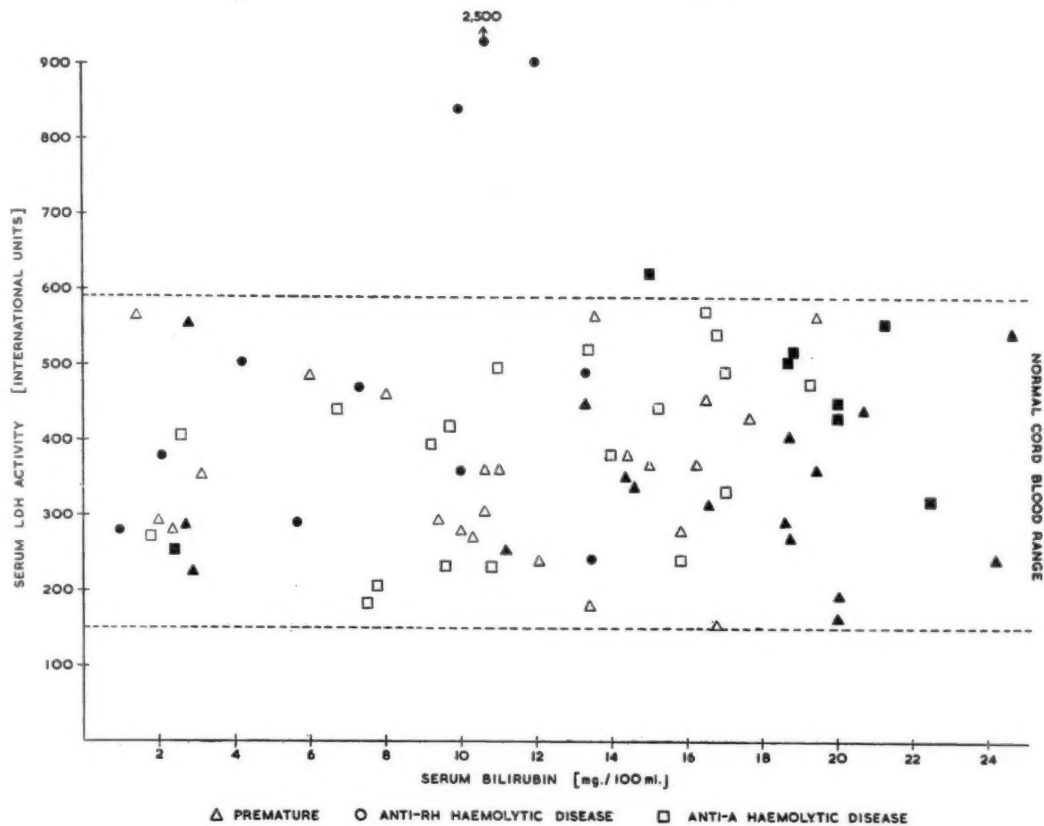


FIG. 3.—Serum LDH activity and bilirubin in prematurity and haemolytic disease. Blackened symbols indicate infants transfused later.

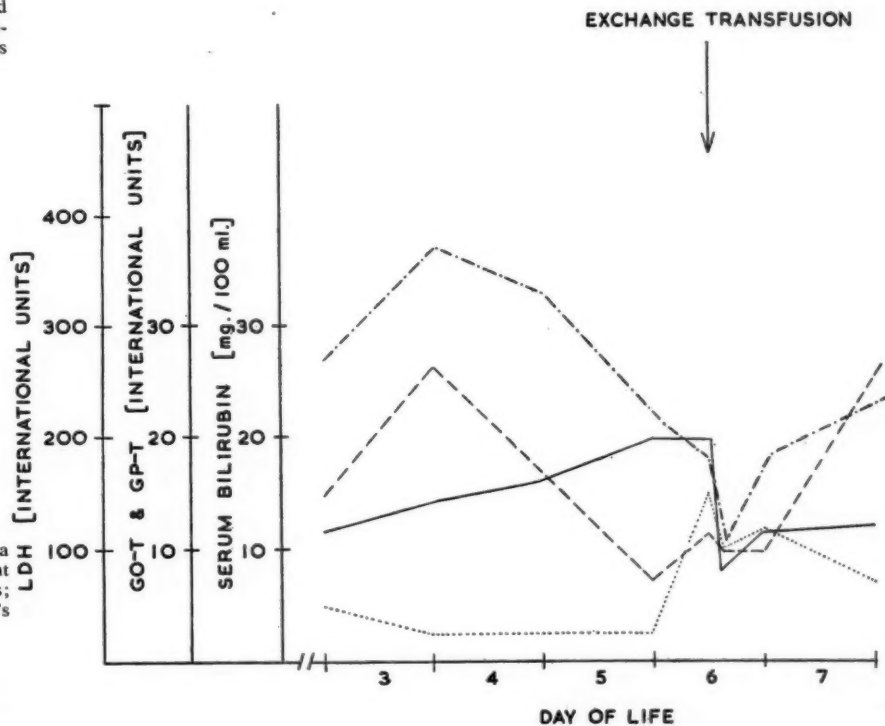


FIG. 4.—Serial enzyme activities in a premature male infant, birth weight 5 lb 3 oz.; gestation, 36 weeks; blood group O Rh negative; mother's blood group O Rh negative.

— serum bilirubin;  
 - - - serum GO-T activity;  
 . . . serum LDH activity;  
 - . . serum GP-T activity.

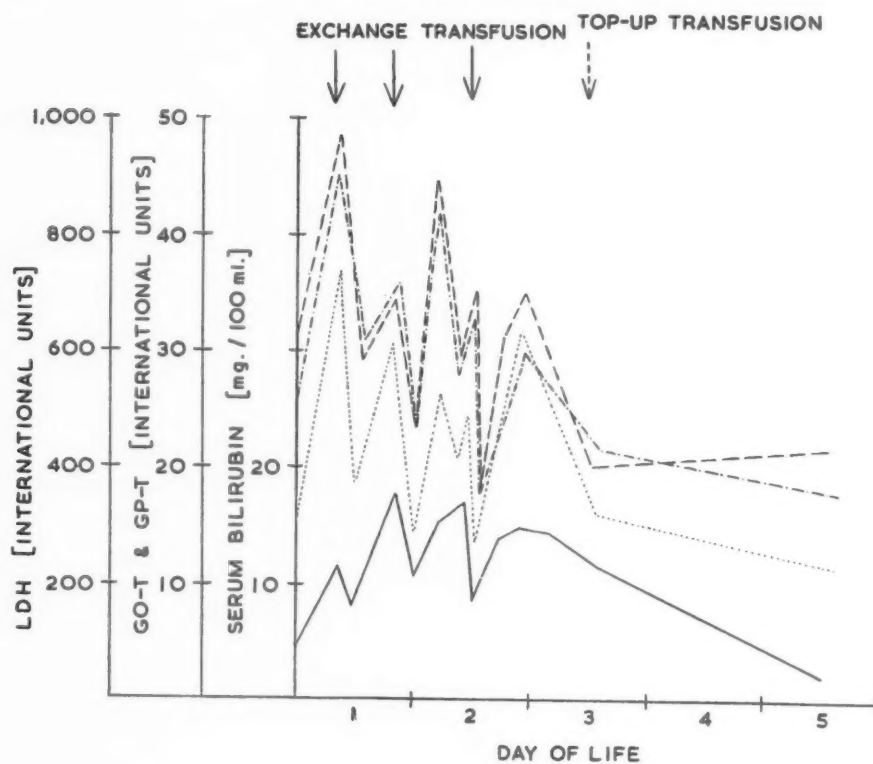


FIG. 5.—Serial enzyme activities in a male infant with anti-Rh haemolytic disease; birth weight 8 lb. 4 oz.; gestation 38 weeks; blood group A Rh positive, mother's blood group A Rh negative.

Key as for Fig. 4.

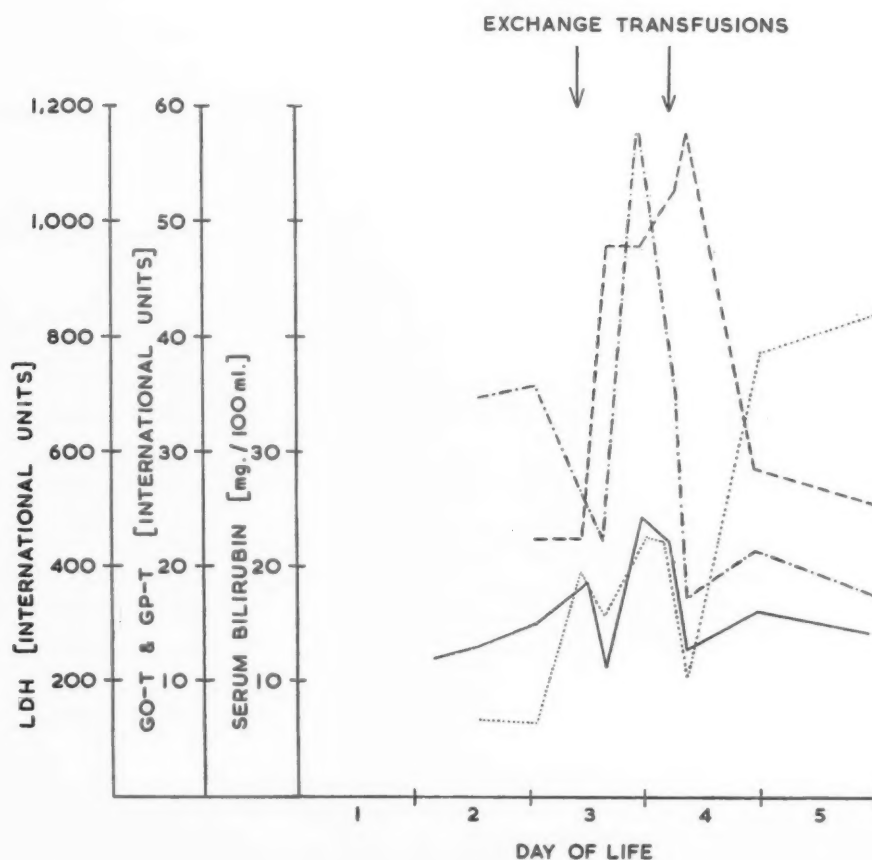


FIG. 6.—Serial enzyme activities in a female infant with anti-A haemolytic disease; birth weight 9 lb. 2 oz.; gestation 40 weeks; blood group A Rh positive; mother's blood group O Rh positive.

Key as for Fig. 4.

## EXCHANGE TRANSFUSIONS

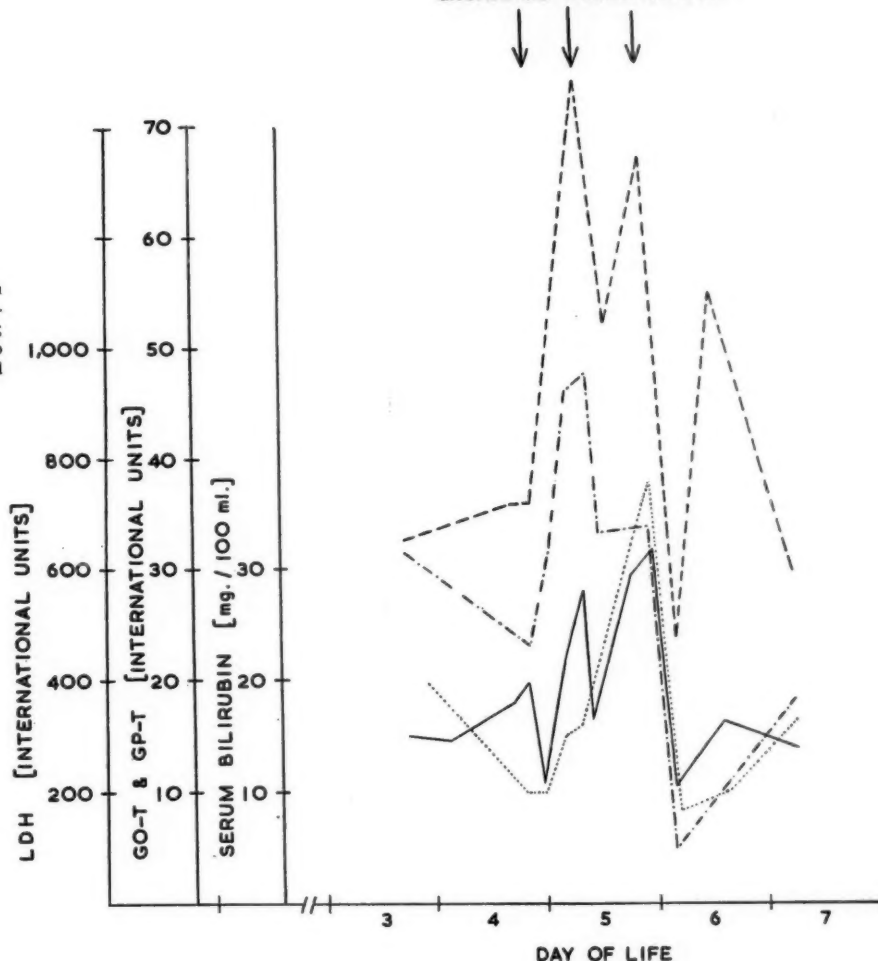


FIG. 7.—Serial enzyme activity in a female infant with anti-A haemolytic disease; birth weight 7 lb.; gestation 40 weeks; blood group A Rh negative, mother's blood group O Rh negative.

Key as for Fig. 4.

and in both cases the enzyme values are increasingly abnormal after transfusion. This is particularly marked in Fig. 7.

The haematological aspect of exchange transfusion in cases of haemolytic disease anti-A is somewhat difficult and the subject of some difference of opinion. In this group it has been the practice to use group O blood of the same Rh group as the baby without washing the cells, so that there is the possibility that immune anti-A has been present in some of the blood used. It is known that immune anti-A can occur in as high a proportion as 10% of blood donors (Walker and Dennis, 1959). It is not known whether immune anti-A was in fact present in any of the bottles used (D. Lehane, personal communication).

The liver dysfunction demonstrated in the cases of haemolytic disease, and which is so much more

obvious in the cases due to anti-A immunization, may be directly related to the disease process. If this should be so it is not surprising that the liver dysfunction is accentuated by transfusion if immune anti-A is present in the transfused blood.

From the practical point of view our experience suggests that there is a good case to be made out for ensuring that the group O blood used for the exchange transfusion of infants suffering from haemolytic disease anti-A is free from immune anti-A.

**Lactate Dehydrogenase and Malate Dehydrogenase.** In all groups there were some LDH and MDH values above normal. The activity of these enzymes may be elevated in liver disease, but more particularly in haemolysis of which this is a very sensitive index. The raised figures which we

obtained in some cases in this investigation appeared to be related to haemolysis in haemolytic disease and were non-contributory in relation to liver function. We do not think, therefore, that the estimation of these enzymes is of any value in the conditions under consideration. Fig. 3 shows LDH values in the three groups under discussion. MDH activity so closely paralleled LDH values in all cases that it has not been treated separately in this study.

### Summary

(1) GO-T, GP-T, LDH and MDH have been estimated in a group of premature babies, and a group of babies suffering from haemolytic disease anti-Rh, and anti-A, with particular reference to liver function. LDH estimation has not been found to be of value in this respect.

(2) Abnormally high values for GO-T and GP-T have been found in a small proportion of the premature group, in a slightly larger proportion of the anti-Rh group, and in an even larger proportion of the anti-A group. A tentative suggestion is made that the liver dysfunction in haemolytic disease anti-A is related to the disease process.

(3) Even more marked abnormality of the enzyme

values occurs after exchange transfusion in the anti-A group. It is postulated that this may be related to immune anti-A in the donor blood. These findings suggest that every effort should be used to see that the group O blood used for exchange transfusion in these cases is free from immune anti-A.

(4) No value attaches to the estimation of LDH or MDH activity in the conditions studied.

We are indebted to Dr. J. E. Horrocks and Dr. J. Ward for much helpful advice and criticism and to Mrs. Mary Robinson for secretarial work. Our grateful thanks are also due to the house surgeons and nursing staff at Risedale Maternity Hospital and the technical staff of the Group Pathology Laboratory, without whose willing co-operation this work could not have been undertaken.

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# ELECTROLYTE PATTERNS IN BANTU BABIES BORN SPONTANEOUSLY AND BY CAESAREAN SECTION

BY

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Great interest has been centred during recent years on the renal physiology and the *milieu intérieur* of newborn infants. However, so far no studies have been carried out on newborn Bantus.

Although it is well established that neonatal renal function is immature (McCance and Young, 1941; McCance, 1959), full-term healthy babies delivered spontaneously and without undue difficulty are known to be able to maintain themselves in satisfactory fluid and electrolyte balance provided that they are adequately fed.

It has, however, been shown that in full-term babies who are delivered only after a difficult labour, and also in premature infants, the blood urea tends to rise to well above the normal value on the second day of life (McCance and Widdowson, 1954; Joppich and Wolf, 1958). How the *milieu intérieur* is affected (if it is affected at all) in babies delivered by caesarean section has, as yet, not been determined.

This study was undertaken (a) to establish the normal values for the blood urea, the serum sodium (Na), chloride (Cl), and potassium (K) and the blood carbon-dioxide combining power (CO<sub>2</sub> combining power) in spontaneously delivered Bantu babies, born at full-term and weighing more than 5½ lb. (normal babies) during the first three days of life; and (b) to determine the serum electrolyte pattern in the first 10 days of life of full-term, healthy Bantu babies delivered by caesarean section (caesarean babies).

## Materials and Methods

From each of 91 normal babies a specimen of approximately 8 ml. blood was taken during the first, second or third day of life. The concentrations of the blood urea, the serum Na, K, and Cl and the CO<sub>2</sub> combining power were measured in each of these specimens. For a variety of reasons a complete set of readings could not be made on every specimen taken. A total of 88 blood urea readings, 84 serum Na readings, 87 serum Cl readings, 82 serum K readings, and 82 CO<sub>2</sub> combining power readings was recorded by the end of the survey. The number of readings made for each electrolyte

during the first, second and third day of life ranged from 26 to 31 (see Tables 1 to 5).

From each of 120 caesarean babies who were clinically well from birth until their discharge from hospital (usually on the tenth day of life) 8 ml. blood were taken on two separate occasions at least 24 hours apart, within their first 10 days of life. The concentration of the blood urea, serum Na, Cl, K and the CO<sub>2</sub> combining power was measured in each of these specimens. Again, for a variety of reasons, a complete set of readings could not always be made on each of the specimens taken. A total of 246 blood urea readings, 254 serum Na readings, 246 serum Cl readings, 226 serum K readings and 226 CO<sub>2</sub> combining power readings was recorded by the end of the survey. The number of readings made for each electrolyte during each of the first seven days of life, and on the tenth day of life in these caesarean babies ranged from 25 to 51. No specimens were obtained on the eighth and ninth days of life.

All the normal babies used in the survey were put to the breast six to 12 hours after delivery and then breast-fed every four hours. All the caesarean babies in the survey received their first feed 12 to 24 hours after delivery and were then breast-fed every four hours.

The specimens of blood were obtained from these infants by venepuncture of either the internal jugular or femoral veins, or from the superior sagittal sinus, the latter being approached via the posterior fontanelle, as described by Kunz (1953). The serum Cl was measured by the method of Schales and Schales (1941), the blood urea by the method of King and Wootton (1956). The CO<sub>2</sub> combining power was estimated by the Van Slyke volumetric method (King and Wootton, 1956), and the serum Na and serum K were measured by flame photometry (King and Wootton, 1956).

The statistical calculations were carried out as follows:

The mean for number (N) of samples was estimated using the formula:

$$\bar{x} = \frac{\sum x}{N}$$

The standard deviation for the individual measurements (the biased estimate of the standard deviation) was determined by using the formula:

$$s = \sqrt{\frac{\sum x^2}{N} - \bar{x}^2}$$

The 95% confidence interval for the various electrolytes was determined using the formula:

$$\bar{x} \pm t_{.95} \frac{s}{\sqrt{N}}, \text{ where } 't'_{.95} \text{ is student's } t.$$

The significant difference tests between the results obtained in normal and in caesarean babies were based on the formula:

$$t = \frac{(\bar{x}_1 - \bar{x}_2)}{\sqrt{\frac{1}{N_1} + \frac{1}{N_2}}} \sqrt{\frac{N_1 S_1^2 + N_2 S_2^2}{N_1 + N_2 - 2}} \text{ distributed as 't' with } n-2 \text{ degrees of freedom.}$$

### Results

**Normal Babies.** Table 1 shows that the mean blood urea for 88 babies, aged from a few hours to 3 days, was 26.7 mg./100 ml. From the first to the second day of life the mean rose slightly (from 24.5 to 28.6 mg./100 ml.), but on the third day of life it had fallen again to 26.8 mg./100 ml.

From Table 2 it can be seen that there was little variation in the mean serum Na between that of the second and third days of life and that the mean for 84 babies in their first three days of life was 135.6 mEq/litre.

Table 3 shows that the mean serum Cl rose from 94.3 mEq/litre on the first day of life to 99.8 mEq/litre on the third day of life. The mean of 87 readings obtained during this period was 96.5 mEq/litre.

The mean serum K was higher on the first day of life than on the two following days when the individual means were approximately identical. The mean for the whole of the three-day period was 4.62 mEq/litre (Table 4).

Table 5 shows that the mean CO<sub>2</sub> combining power in 82 babies during the first three days of life was 19.7 mEq/litre, the mean being slightly higher on the first day of life than on each of the following days.

**Caesarean Babies.** Fig. 1 and Table 6 show that the blood urea rose from a mean of 32.9 mg./100 ml. on the first day of life to 44.1 mg./100 ml. on the fourth day, and then fell slowly to 32.5 mg./100 ml. on the seventh day and 17.6 mg./100 ml. on the tenth day.

From Table 7 it can be seen that the mean serum Na showed no definite trend during the first 10 days of life, ranging from 132 mEq/litre on the first day to 138 and 137 mEq/litre on the third and fifth days respectively, and to 134.7 mEq/litre on the tenth day.

Table 8 shows that the mean serum Cl was 98.6 mEq/litre on the first day of life. After falling to 96.3 mEq/litre on the second day, it rose steadily

TABLE 1  
BLOOD UREA IN NORMAL BABIES DURING FIRST THREE DAYS OF LIFE

Day	No. of Samples	Arithmetic Mean (mg./100 ml.)	Standard Deviation (mg./100 ml.)	95% Interval for $\bar{x}$ (mg./100 ml.)
1	31	24.5	9.0	21.2-27.8
2	30	28.6	9.5	25.0-32.2
3	27	26.8	12.6	21.8-31.8
1-3	88	26.7		

TABLE 2  
SERUM SODIUM IN NORMAL BABIES DURING FIRST THREE DAYS OF LIFE

Day	No. of Samples	Arithmetic Mean (mEq/litre)	Standard Deviation (mEq/litre)	95% Interval for $\bar{x}$ (mEq/litre)
1	30	134.8	5.2	132.8-136.7
2	29	136.3	4.3	134.7-138.0
3	25	136.1	4.0	134.4-137.7
1-3	84	135.6		

TABLE 3  
SERUM CHLORIDES IN NORMAL BABIES DURING FIRST THREE DAYS OF LIFE

Day	No. of Samples	Arithmetic Mean (mEq/litre)	Standard Deviation (mEq/litre)	95% Interval for $\bar{x}$ (mEq/litre)
1	30	94.3	4.5	92.6-95.9
2	30	95.8	6.2	93.5-98.2
3	27	99.8	5.1	97.8-101.9
1-3	87	96.5		

TABLE 4  
SERUM POTASSIUM IN NORMAL BABIES DURING FIRST THREE DAYS OF LIFE

Day	No. of Samples	Arithmetic Mean (mEq/litre)	Standard Deviation (mEq/litre)	95% Interval for $\bar{x}$ (mEq/litre)
1	29	4.94	0.80	4.64-5.25
2	29	4.55	0.49	4.36-4.74
3	24	4.5	0.67	4.22-4.78
1-3	82	4.62		

to 104 mEq/litre on the sixth day, only to fall again over the period of the next four days to the mean value of 97.5 mEq/litre on the tenth day.

Table 9 shows that the mean serum K was markedly higher on the first day of life (5.13 mEq/litre) than on each of the following nine days. On the second day the mean serum K dropped sharply to 4.5 mEq/litre and then remained fairly

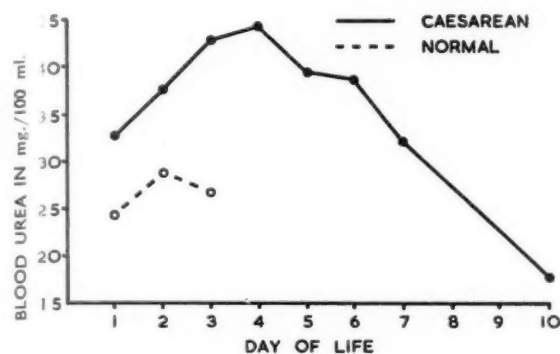


FIG. 1.—Changes in concentration of blood urea during first 10 days of life.

TABLE 5

CO<sub>2</sub> COMBINING POWER IN NORMAL BABIES DURING FIRST THREE DAYS OF LIFE

Day	No. of Samples	Arithmetic Mean (mEq/litre)	Standard Deviation (mEq/litre)	95% Interval for $\bar{x}$ (mEq/litre)
1	26	20.11	3.00	18.9–21.3
2	30	19.71	2.72	18.69–20.73
3	26	19.45	3.66	17.97–20.93
1–3	82	19.79		

TABLE 6

CHANGES IN THE CONCENTRATION OF UREA IN THE BLOOD DURING THE FIRST 10 DAYS OF LIFE IN CAESAREAN BABIES

Day	No. of Samples	Arithmetic Mean (mg./100 ml.)	Standard Deviation (mg./100 ml.)	95% Confidence Interval for $\bar{x}$ (mg./100 ml.)
1	48	32.9	16.6	28.1–37.7
2	30	37.7	16.5	31.6–43.8
3	30	42.4	25.3	33.0–51.8
4	25	44.1	28.4	28.3–59.8
5	29	39.5	24.5	30.2–48.8
6	29	38.3	23.6	29.3–47.3
7	25	32.5	36.8	17.3–47.7
10	30	17.6	6.4	15.2–20.0

constant during the next four days. On the seventh day it rose to 4.85 mEq/litre, and the mean serum K on the tenth day was the same as that on the seventh day.

Table 10 shows that the mean CO<sub>2</sub> combining power was at its highest (19.5) during the first day of life. It then fell steadily to 17.4 on the fourth day. After this it showed an overall tendency to rise, reaching 18.3 on the seventh day, this also being the approximate value for the tenth day.

The significant difference tests between the electro-

TABLE 7

CHANGES IN CONCENTRATION OF SERUM SODIUM DURING THE FIRST 10 DAYS OF LIFE IN CAESAREAN BABIES

Day	No. of Samples	Arithmetic Mean (mEq/litre)	Standard Deviation (mEq/litre)	95% Confidence Interval for $\bar{x}$ (mEq/litre)
1	51	132.0	6.4	130.2–133.8
2	28	135.8	5.4	133.7–137.9
3	30	138.0	4.0	136.5–139.5
4	34	134.8	4.8	132.1–137.6
5	29	137.1	6.0	134.9–139.7
6	29	132.9	7.2	130.1–135.6
7	25	135.6	4.4	133.8–137.4
10	28	134.7	5.4	133.7–135.7

TABLE 8

CHANGES IN CONCENTRATION OF SERUM CHLORIDE DURING THE FIRST 10 DAYS OF LIFE IN CAESAREAN BABIES

Day	No. of Samples	Arithmetic Mean (mEq/litre)	Standard Deviation (mEq/litre)	95% Confidence Interval for $\bar{x}$ (mEq/litre)
1	48	98.4	5.4	96.8–100.0
2	30	96.3	5.3	94.3–98.6
3	30	97.8	4.8	96.0–99.6
4	25	98.1	6.6	94.4–101.7
5	28	100.6	4.7	98.8–102.4
6	30	104.5	7.0	101.9–107.2
7	25	103.3	7.0	100.4–106.2
10	30	97.4	6.0	95.2–99.7

TABLE 9

CHANGES IN CONCENTRATION OF SERUM POTASSIUM DURING THE FIRST 10 DAYS OF LIFE IN CAESAREAN BABIES

Day	No. of Samples	Arithmetic Mean (mEq/litre)	Standard Deviation (mEq/litre)	95% Confidence Interval for $\bar{x}$ (mEq/litre)
1	45	5.13	1.00	4.83–5.43
2	27	4.41	0.88	4.06–4.76
3	26	4.52	0.84	4.18–4.86
4	25	4.56	0.90	4.04–5.08
5	27	4.37	0.85	4.03–4.71
6	26	4.43	0.82	4.10–4.76
7	25	4.84	0.80	4.51–5.17
10	25	4.82	0.76	4.50–5.14

TABLE 10

CHANGES IN VALUE OF BLOOD CARBON DIOXIDE COMBINING POWER DURING THE FIRST 10 DAYS OF LIFE IN CAESAREAN BABIES

Day	No. of Samples	Arithmetic Mean (mEq/litre)	Standard Deviation (mEq/litre)	95% Confidence Interval for $\bar{x}$ (mEq/litre)
1	41	19.46	3.31	18.43–20.53
2	29	18.76	2.77	17.70–19.81
3	27	17.68	2.64	16.63–18.72
4	25	17.43	3.27	15.62–19.23
5	26	18.08	3.94	16.49–19.68
6	25	17.52	3.70	15.99–19.04
7	25	18.36	4.81	16.38–20.34
10	28	18.40	4.43	16.68–20.12

TABLE 11

COMPARISON OF ELECTROLYTES OF BANTU AND NON-BANTU BABIES

Electrolyte Means	Bantu Babies	Non-Bantu Babies (Gottfried <i>et al.</i> , 1954)	Non-Bantu Babies (Spivek, 1956)
Urea (mg./100 ml.) ..	26.7	—	20
Na (mEq/litre) ..	135.6	143	149
Cl (mEq/litre) ..	96.5	111	105.5
K (mEq/litre) ..	4.62	—	—
CO <sub>2</sub> combining power (mEq/litre) ..	19.74	20.5	23

lyte values of caesarean and normal babies showed the following:

**Urea.** The mean blood urea during the first day of life is significantly higher (significant at 1/1,000 level) in caesarean babies (34.8 mg./100 ml.) than in normal babies (24.2 mg./100 ml.).

**Serum Na and Cl.** During the first day of life the serum Na and Cl in caesarean babies are significantly higher (significant at the 1/1,000 level) than in normal babies. However, on the second and third days these differences are no longer present.

**Serum K.** On none of the first three days of life is there a significant difference between the mean serum K of caesarean babies and that of normal babies.

**CO<sub>2</sub> Combining Power.** The CO<sub>2</sub> combining power is significantly lower (significant at 5/100 level) in 3-day-old caesarean babies than in 3-day-old normal babies. During the first two days of life, however, there is no significant difference between the two groups.

The relevant tests showed no significant difference between electrolyte values of caesarean babies aged 0 to 12 hours and those aged 12 to 24 hours.

### Discussion

Although the mean electrolyte values obtained in our series may be regarded as fairly representative of the Bantu community where this work was carried out, it should, however, be emphasized that our results are strictly applicable only to newborn babies whose electrolyte estimations are carried out in the laboratory serving the hospital in which the present survey was made. Possibly because of this limiting factor, we are unable to draw any conclusions from a comparison between the values obtained in our series and those obtained in two similar series (Spivek, 1956; Gottfried, Bogin and Levycky, 1954) carried out on babies of

European extraction, the results in all these series differing markedly from one another (Table 11).

From the significant difference tests carried out between the electrolyte values of the normal babies and the caesarean babies in our series, it can be seen that the most striking feature is the difference in the behaviour of the blood urea, the mean blood urea in caesarean, on each of the first three days of life, being significantly higher (significant at 1/1,000 level) than that of normal babies during a corresponding period.

Furthermore, the mean blood urea in caesarean babies continued to rise until it reached an 'abnormally' high level on the fourth day of life, although all the infants remained clinically well. By the tenth day it had, however, fallen markedly, the mean value being almost identical to that found in normally delivered 9-day-old babies (McCance and Widdowson, 1947).

In contrast, the blood urea in our normally delivered babies, having risen initially, began to fall on the third day and remained well within 'normal' limits during the period of investigation, which agrees with the findings elsewhere in the literature (McCance and Widdowson, 1947).

In an attempt to explain the difference in the behaviour of the blood urea between the two groups, one may neglect the fact that their feeding schedules were slightly dissimilar during the first 24 hours of life; although the normal babies received two extra feeds in this period, the extra fluid intake from these was negligible, as mothers only begin to secrete milk freely on the third day after delivery.

The behaviour of the blood urea in the caesarean babies in this series is very similar to that found in premature infants, and also in babies delivered by forceps after a difficult labour (McCance and Widdowson, 1954; Joppich and Wolf, 1958). As in the latter group, the reason for the rising blood urea in infants born by caesarean section is a forced degradation of the tissue proteins. This appears to commence at, or even before delivery, as there is no significant difference between the mean blood urea for the first 12 hours of life and that of the second. In some of these babies it is possible that there may also have been an associated low renal function.

The possible reasons for the forced tissue breakdown have been discussed in the literature (McCance, 1959; McCance and Widdowson, 1954).

### Summary

The mean values for the blood urea, the serum Na, Cl, and K, and the CO<sub>2</sub> combining power

were determined on each of the first three days of life in 91 babies delivered *per vaginam*.

The mean values for the blood urea, the serum Na, Cl, and K, and the CO<sub>2</sub> combining power were determined on the first, second, third, fourth, fifth, sixth, seventh and tenth days of life in a group of caesarean babies.

In the caesarean babies the mean blood urea tended to rise from the first to the fourth day of life, reaching 'abnormally high levels'. It then gradually fell so that by the tenth day of life its value was similar to that obtained from a group of normally delivered babies of the same age.

On each of the first three days of life the mean blood urea was shown to be significantly higher in caesarean than in normally delivered babies.

The behaviour of the blood urea was found to be similar to that of premature infants and those delivered by forceps after a difficult labour.

The reasons for the rising mean blood urea are briefly discussed.

My thanks are due to Dr. C. Lavery for permission to carry out this survey in his obstetrical ward; to Dr.

R. Cassel and the staff of the Baragwanath Hospital biochemistry laboratory, who did all the electrolyte estimations; to Miss S. Niven for help with the statistics; to Dr. S. B. Dimson, who was good enough to criticize this paper and to Drs. E. Kahn and S. Wayburne in whose Paediatric Units this work was carried out.

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# ARGININOSUCCINIC ACIDURIA

## AN INBORN ERROR OF AMINO ACID METABOLISM

BY

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It is probable that many, if not all, of the inherited ('inborn') metabolic disturbances result from a specific enzyme defect, arising from a single abnormal gene. Examples are now known of a number of such inherited defects, some involving amino acids, which result in a block of a metabolic pathway. For example, the normal pathway for the metabolism of phenylalanine and tyrosine is by a series of conversions, each mediated by a specific enzyme. The lack of any one of these enzymes will lead to a specific disease and at least four such diseases have been identified, the most common of which is phenylketonuria.

Similar enzyme deficiencies involving the metabolism of amino acids are, however, still very uncommon. A new instance has been recorded by Allan, Cusworth, Dent and Wilson (1958). They have described two sibs, suffering from mental retardation, who excreted in the urine large amounts of an amino acid not normally present. Later Westall (1960a, b) identified this substance as argininosuccinic acid, a known intermediate in the bio-synthesis of urea. The condition must be rare, since Allan *et al.* (1958) stated that 1,500 mentally deficient patients were screened and no further examples discovered.

This paper records an infant with an identical abnormality, detected within a month of birth in December 1958, and the only other example of this type so far described. A metabolic disorder was suspected because clinical examination and routine pathological investigations had revealed no obvious cause for a sudden onset of severe illness in the first week of life. Paper chromatography of the urine showed a gross amino aciduria due to the presence of large amounts of an amino acid and some progress had been made towards identifying the amino acid before the article by Allan *et al.* (1958) was noted. The similarity between the properties of the amino acids in their cases and ours led us to suspect that they were identical, and this was later proved by

comparison with a specimen of argininosuccinic acid (ASA) isolated from the published cases and kindly provided by Dr. Westall.

The detrimental effect on this infant of his metabolic disorder, and the history of the two earlier cases, indicated the desirability of early investigations which might provide a pointer for rational dietetic therapy such as that now in use in certain other inherited metabolic disturbances. Some such investigations are described in this paper, but so far they have not paved the way for treatment.

### Case Reports

**Two Cases Previously Described.** The two cases described by Allan *et al.* (1958) were sibs, a girl, M., and a boy, K., coming under observation at the ages of 3 years and 5 months and 6 years and 3 months, respectively. The parents were not consanguineous. Of their five children, the first and third were normal; the fifth apparently had kernikterus as a baby and had had an exchange transfusion for Rh (D) incompatibility; he died of bronchopneumonia at 4½ months of age.

Both the sibs, M. and K., with amino-aciduria, were mentally defective when first examined, but in neither case did the neonatal history suggest the likelihood of kernikterus. M.'s Gesell rating was 32 and K.'s rating on the Terman-Merrill scale was 50. M. had a moderate amount of vomiting in her early months, and after the age of 2 suffered from convulsions, for which she was admitted to hospital at the age of 3 years and 5 months. After these convulsions, there was a period of severe incoordination when she was unable to feed herself or stand. K. had never had convulsions, but electroencephalography 'showed definite evidence of epilepsy'. The two children had a similar facial appearance and a 'sad and wistful' expression. Both had similar hair, dry and friable and giving a matted appearance. M.'s skin was slightly rough on the arms and dorsum of the hands. K.'s skin texture was normal. Both children had systolic murmurs, possibly due to an interventricular septal defect.

According to their mother, whose intelligence was 'above average', both children appeared normal during

TABLE 1  
BIOCHEMICAL FINDINGS IN PLASMA OR SERUM

	First Month (1)	9 Months (2)	10 Months (Acutely Ill) (3)	13 Months (4)
Sodium (mEq per litre) .. .. .	142	138	131	133
Potassium (mEq per litre) .. .. .	5.4	3.6	4.6	4.5
Carbon dioxide capacity (mEq per litre) .. .. .	22	—	22	—
Chloride (mEq per litre) .. .. .	105	105	100	105
Urea (mg. per 100 ml.) .. .. .	44	13	27	14
Non-protein nitrogen (mg. per 100 ml.) .. .. .	56	27	66	26
Total protein (g. per 100 ml.) .. .. .	5.5	5.24	4.4	6.89
Albumin (g. per 100 ml.) .. .. .	3.6	3.45	—	4.25
Globulin (g. per 100 ml.) .. .. .	1.9	1.79	—	2.64
Serum bilirubin (mg. per 100 ml.) .. .. .	—	—	2.5	0.5
Thymol turbidity (units) .. .. .	2.5	3	1	2
Thymol flocculation .. .. .	Negative	Negative	Negative	Negative
Zinc sulphate turbidity (units) .. .. .	—	—	2.5	1.5
γ-globulin turbidity (units) .. .. .	5	4	5	5
Calcium (mg. per 100 ml.) .. .. .	10.1	9.9	7.0	10.2
Phosphate (mg. per 100 ml.) .. .. .	7.2	2.3	1.2	6.3
Phosphatase (K.A. units) .. .. .	18.1	22.7	27.2	21.4
S.G.O.T. (units) .. .. .	—	46	196	78
S.G.P.T. (units) .. .. .	—	46	132	74
Blood sugar (mg. per 100 ml.) .. .. .	54	—	126	—
Cholesterol (mg. per 100 ml.) .. .. .	202	70	110	—
Fatty acid esters (mg. per 100 ml.) .. .. .	925	—	—	—

the first year of life. M. was a 'lovely, bonny, happy baby' with normal hair. K. thrived well and until 15 months old had 'beautiful curly hair'. M. sat up at 8 months and walked at 11 months. K. sat up at 8 months and walked at 13 months.

No mention of liver enlargement or abdominal distension was made in either child. The level of alkaline phosphatase was moderately high, but apart from this, liver function, so far as assessed, was not disturbed. Both sibs excreted large amounts of ASA in the urine. This substance was present in higher concentration in the cerebrospinal fluid than in the plasma. This disorder of amino acid metabolism was not present in any other member of the family.

**Present Case.** The case investigated by us differed in various respects from the two already described.

**First Three Months of Life.** J., a boy, was born in hospital on December 24, 1958, after a normal pregnancy and delivery, birth weight 8 lb. 11 oz. The parents were not consanguineous and J. was the first child. He was noted to have been 'cyanosed for 2 minutes after birth'. He was breast fed and appeared normal until 5 days old, when he sucked badly. The next day his abdomen rapidly became distended, though the stools were normal. He was apathetic; his weight then was 8 lb., his rectal temperature 94° F. There was some nasal obstruction, his respirations were rapid (probably due to his distension) and there were some signs at the base of the lungs. He was admitted that evening to the Queen Elizabeth Hospital for Children. Radiographs showed gaseous distension of the bowel, but revealed no pulmonary lesion. Next day, at 7 days of age, he was unconscious with occasional convulsive movements of the right arm. There was oedema of the ankles; he vomited five times and the vomit contained altered blood. The liver was felt and was possibly enlarged, but abdominal distension made palpation difficult. The white blood cell count

was 26,200 per c.mm. (polymorphs 44%, eosinophils 1%, lymphocytes 53%, monocytes 2%). Plasma electrolyte levels were within normal limits (Table 1, column 1), and the cerebrospinal fluid appeared normal on routine examination. He was given a glucose electrolyte mixture by tube as he could not suck. The vomiting diminished and at 11 days he was able to take a half-cream dried milk mixture with sugar. At 3 weeks the liver was enlarged to the level of the umbilicus. Liver function tests were, however, normal. Chromatography of the urine showed that an unknown amino acid was being excreted in large amounts and one with similar R<sub>f</sub> value was present in the cerebrospinal fluid. This amino acid was later proved to be argininosuccinic acid (see below). Thereafter, liver enlargement and abdominal distension were always present, although in varying degree. At the age of 3 months the liver edge was firm and hard.

There was intermittent vomiting until he was over 2 months of age. His weight at 4 weeks was about average for his birth weight according to our assessment (Levin, Mackay, Neill, Oberholzer and Whitehead, 1959), but thereafter his gains were irregular and inadequate. He was inactive, often fretful and he suffered from recurrent otorrhoea. There was occasional slight oedema of the feet and ankles and the skin tended to be patchily rough and dry. The degree of his alertness varied considerably, probably inversely with his malaise, but he was late in reaching every milestone.

#### Dietetic Changes

(a) PROTEIN-FREE DIET FOR ONE WEEK. It seemed reasonable to postulate that the child's illness and retardation were due to a toxic effect of argininosuccinic acid and that by analogy with the treatment of phenylketonuria, improvement would occur if the production of the amino acid could be reduced. Therefore, as a preliminary investigation towards this end, the effect

TABLE 2  
URINARY EXCRETION OF ARGININOSUCCINIC ACID AND UREA

Diet	Protein (or Equivalent) Intake (g./day)	Total Nitrogen (mg.)	Urea Nitrogen (mg.)	ASA Nitrogen (mg.)	ASA Nitrogen As % of Total Nitrogen	ASA Nitrogen As % of Urea Nitrogen	ASA Excretion (g./day)
Half-cream national dried milk .. ..	36	3,445	2,500	571	16.6	22.8	3.0
No protein .. ..	..	262	138	112	43	81	0.6
Synthetic amino acids .. ..	10	860	394	326	39.2	81	1.65
Casein hydrolysate with low arginine content .. ..	15	1,261	659	364	29	55	1.9*
As above + 2 g. arginine .. ..	17	1,235	613	381	31	62	2.0*
As above + 3 g. arginine .. ..	18	1,867	848	598	32	72	3.1

\* Mean of three days.

of removal of protein from the diet on the formation of argininosuccinic acid, as assessed by its excretion in the urine, was investigated. Hence, at 3½ months of age, the infant's half-cream dried milk mixture was replaced by a protein-free mixture providing an equivalent number of calories and composed of gluten-free flour, sugar and arachis oil, together with salt and adequate amounts of vitamins A, B, C and D. Although just after the change in diet there was a recurrence of otorrhoea, within five days the abdominal distension was strikingly diminished, the liver became smaller, and the excretion of argininosuccinic acid fell by 80% (Table 2). On the other hand, the gums had become red, appetite failed and by the seventh day there were skin changes, widespread and extensive patchy dry erythematous areas, with intertrigo and angular stomatitis. The infant was fretful and had lost 16 oz. in seven days. The dried milk feeds were then restarted, the skin began to improve within 24 hours and soon the appetite was good; eight days later the abdominal distension was again gross and the liver reached nearly to umbilical level. The changes in the baby's condition seemed directly related in time to the changes in diet.

(b) DRIED MILK DIET. At 4 months of age, 11 days after half-cream dried milk was restarted, the infant was sucking and much more contented. He weighed 12½ lb. and had more than regained his loss in weight on the protein-free diet. He was, however, only about 3½ lb. over birthweight and over 3 lb. below our expected average weight for infants weighing 8 to 9 lb. at birth (Levin *et al.*, 1959). His diet was changed to full-cream dried milk and sugar, and in the next few days he relapsed, with loss in weight, redness of gums and angular stomatitis and worsening of the skin condition—only to improve again, this time without change in the diet.

At 5 months the infant weighed only 12 lb. 5 oz., was retarded in all his attainments and was thought to be of subnormal intelligence. An assessment was attempted by Dr. Agatha Bowley when the infant was 4 months and 11 days, and she considered his reactions were those of a 2-month baby.

(c) ARGININE-FREE DIET, FOLLOWED BY DRIED MILK DIET. At 5½ months of age, an attempt was made to assess the effect of complete elimination of arginine from the diet. For this, a synthetic amino acid mixture, containing the eight essential amino acids together with

additional glycine to make up nitrogen requirement, was utilized. To provide adequate calorie intake, cane sugar, lactose and gluten-free flour were also given. Although he lost some weight and his liver enlarged a little, he was otherwise unchanged, but a week after the commencement of the new diet, he became fretful and miserable and gradually became unconscious. He was tube fed with a glucose electrolyte mixture and improved within 24 hours and a normal diet was gradually reintroduced. He began to gain weight again, his liver diminished in size but he developed a number of indolent pustules on the scalp.

During the next two months the infant made better progress. He gained weight and the scalp condition was greatly improved, although the ulcers did not heal completely. By 7½ months he weighed about 17½ lb. and had cut two teeth and a month later a further two.

(d) DIETS VARYING IN ARGININE CONTENT. Despite the unsatisfactory response to the synthetic amino acid mixture, a further endeavour was made to assess the effect of low and high arginine diets. Accordingly, when the infant was 9 months old, and weighed 18 lb. 1½ oz., he was taken off ordinary feeds and given a casein hydrolysate preparation, from which about half the arginine had been removed. There was little change in his condition during the next fortnight, except that an upper respiratory tract infection developed, his skin condition tended to deteriorate and he lost a little weight. As it was thought that there might be a relative deficiency of lysine and tryptophan in his diet, these were now added to his feeds. After 12 days on the casein hydrolysate preparation, arginine was added for a period of 17 days, giving at first 2 g. and, for the last four days, 3 g. of arginine per day. The liver altered little in size, but the scalp condition improved. The effect of the alteration in arginine intake on ASA excretion is discussed below. Three days later, whilst he was still being fed on the casein hydrolysate, but without added arginine, an episode of serious illness began with fluctuating severity, necessitating many rapid changes in treatment. It commenced with a urinary infection (*Esch. coli*) treated with chloramphenicol and neomycin. Eight days later, he began to refuse feeds and to vomit, the liver became larger and he had occasional jerking movements of the elbows and there was a tendency for the head to deviate to the right. By next day he was worse

and, since vomiting increased in severity, glucose-saline was given by the intravenous route. Liver function tests (Table 1, column 3) showed only a moderate degree of impairment. His condition worsened, he became spastic on the right side and began to have Jacksonian convulsions, affecting the same side, for which he was treated with paraldehyde. On the same day large amounts of blood were aspirated from the stomach and he was given a blood transfusion. At times he could barely be roused. However, he improved and began to take fluids by mouth, but marked oliguria developed. Because of this and a persistent oedema, he was given only arachis oil and glucose by mouth and a restricted fluid intake. This treatment was continued for 11 days, with the gradual substitution during the last six days of unsweetened half-cream dried milk, with sugar added. Since oedema persisted, he was given Edosol (low sodium dried milk) and continued on this for 10 days, after which the ordinary milk feeds were restored, with the addition of cereal and apple puree. The oedema gradually diminished. A month after the commencement of this episode of acute illness, he returned to his usual state of health. His weight was somewhat less than it had been one month earlier. His liver was still enlarged to the level of the umbilicus and his skin was still scaly, dry and 'spotty'. When he was nearly 10 months, Dr. Bowley considered him to have the developmental picture of a 7- to 8-month-old baby.

He began to gain weight more satisfactorily and remained relatively well apart from a slight upper respiratory infection. When he was discharged from hospital on February 24, 1960, age 14 months, his weight was 20 lb. 4½ oz.

**Second Admission.** He was readmitted on May 31, at the age of 17 months, having had seven convulsions on the previous days, with twitching of the arms and legs. These episodes lasted for only one minute, without loss of consciousness and without vomiting. The enlargement of the liver and the condition of his skin were unchanged. The fits continued in diminished number after admission, and were controlled with phenobarbitone and epanutin. Examination of the cerebrospinal fluid obtained 16 days after admission, when the fits had ceased, revealed an increased cell count (102 lymphocytes per c.mm.). The complement fixation tests for lymphocytic choriomeningitis and mumps virus, and the leptospiral agglutination tests, were negative. His stay in hospital was prolonged by a sequence of chest and skin infections for which he was treated with antibiotics. He was discharged on September 6, 1960, aged 20 months, weighing 2 lb. 12 oz., having lost 1 lb. 5 oz. during his 14 weeks' stay in hospital. At 15 months he was able to pull himself up, and stand with support, and at 21 months he began to walk with support. When he was 18 months Dr. Bowley considered him to have a developmental age of about 12 months. Encephalography was also carried out at this time and Dr. B. Gordon reported as follows:

'The dominant activity in the parieto-occipital region is regular and symmetrical at 5-6 c/s. No

other significant activity is seen either when the child is awake or during a period of sleep. The E.E.G. is normal for the age.'

**Third Admission.** Two months after discharge, the patient was admitted for a third time on November 7, 1960, having had five convulsions of short duration during the previous 12 hours. The convulsions consisted of generalized twitchings with cyanosis. His tonsils were enlarged and inflamed, he had a temperature of 103.7° F. with raised pulse and respiratory rates. One further convulsion occurred after admission. Treatment with penicillin was followed by an erythematous rash. This disappeared when the antibiotic was withdrawn and pheneregan given. The infection finally yielded to terramycin. In view of the fits, long-term anticonvulsant therapy with phenobarbitone was prescribed. He was discharged on November 24, 1960. There had been little or no change in the size of the liver nor in the skin condition.

**Present State.** The child is now (March 1961) 2½ years of age, weighs 25 lb. 4 oz. and is mentally much retarded. He can only stand if supported and understands no words. The gross liver enlargement and the roughness of the skin persist. The hair still has a brittle character, but the finger-nails and toe-nails are now apparently normal.

**Family History.** There was no history of fits, mental defect or other relevant disease in the parents, grandparents and other relatives of the mother, nor in the only two relatives of the father who are known to him.

**Hair.** A specimen of hair was kindly examined by Dr. A. Jarrett, who reports as follows:

'The hair shows breaks of the trichorrhexis nodosa type involving mainly the fine type of hair. The colour fluorescence of the breaks with acridine orange is red and this indicates a metabolic abnormality of the hair keratin.'

**Comparison of the Present Case with the Two Previously Described.** The three patients, for the sake of clarity, are indicated below by the following letters: present case, J.; previously described cases, girl sib, M., her brother, K.

All three patients were excreting large amounts of ASA and had higher concentrations of this amino acid in the cerebrospinal fluid than in the plasma. All three appeared normal at birth. J. showed some symptoms at 6 days of age, whereas M. and K. were apparently symptom-free during their first year. All are now mentally retarded; J. and M. suffer from fits and K. has an electroencephalogram indicating epilepsy. All three appear to have a facial resemblance to one another (Fig. 1), and have brittle hair. J. suffered from extensive lesions of the skin and buccal mucous membrane and had brittle toe-nails and finger-nails. M. had some localized roughness of the skin; K. has normal skin texture.



FIG. 1.—Appearance of child at 17 months.

Striking features in J.'s condition are gross enlargement of the liver, abdominal distension and poor physical progress, with periods of apathy and fretfulness. He has also had periods of unexplained unconsciousness. None of these figure in the history of the two sibs. On the other hand, he has no abnormal cardiac findings, and M. and K. have systolic murmurs, presumably indicating a cardiac lesion.

A raised alkaline phosphatase level has been found in all three patients, and J. has had definite evidence of liver dysfunction. It may be that the raised alkaline phosphatase level found in M. and K. indicate liver dysfunction in the sibs also.

**Biochemical Findings and Liver Function Tests.** Some relevant biochemical findings are summarized in Table 1. The findings, including the liver function tests, were normal shortly after admission (column 1), i.e. in the first month of life, though during this period the alkaline phosphatase fluctuated between 18.1 and 32.7 King-Armstrong units per 100 ml. Column 2 shows the findings at 9 months of age whilst the infant was having casein hydrolysate from which half of the arginine had been removed, and just before the severe episode of illness already described. Liver function tests were still within normal limits despite the grossly enlarged liver. The only abnormality found was a very low serum phosphorus, due to the low phosphorus content of the casein hydrolysate preparation. Column 3 gives the findings 24 days later at the worst phase of this episode of illness, when the infant was 10 months old; the serum transaminases by then indicated some impairment of liver function, and in addition both alkaline phosphatase and serum bilirubin levels were raised. Again, as a result of the low dietary phosphorus, serum phosphorus and calcium levels were low. Column 4 gives the findings at about 13 months of age, after recovering from the acute symptoms of this period; the serum transaminases were still slightly raised, but all other biochemical findings had returned to normal.

#### Laboratory Investigations

**Paper Chromatography.** Urine (0.005 ml.) was applied to the paper, undiluted and untreated, using butanol-acetic acid-water and phenol-ammonia as solvent systems. The amino acids were detected with a cadmium acetate-ninhydrin reagent (Heilmann, Barrolier and Watzke, 1957) prepared by dissolving 100 mg. cadmium acetate in a mixture of 10 ml. water and 5 ml. glacial acetic acid and making up to 100 ml. with acetone. To this solution 1 g. ninhydrin was added before use. The paper chromatogram was dried, dipped into the reagent, and allowed to remain in the dark for 24 hours in an ammonia-free atmosphere.

Two-way chromatography (Fig. 2) using the above solvent systems, as well as one-way chromatography of fresh urine using butanol-acetic acid-water, usually revealed only one intense ninhydrin-positive band ( $R_F$  value 0.11 in butanol-acetic acid-water) due to the presence of argininosuccinic acid, in addition to the amino acids normally seen in urine. Sometimes, however, a small band of  $R_F$  0.06 due to an anhydride of the acid, was detected close to the main ASA band. Two bands were also detected with phenol-ammonia-water, the main one being the ASA fraction of  $R_F$  value 0.27 and the other, a much smaller one of  $R_F$  value 0.49 corresponding to an anhydride (Ratner, Petrack and Rochovansky, 1953); occasionally, if the urine had been standing at room temperature for some time, a considerable degree of conversion into the anhydride occurred and two fractions of equal intensity were obtained.

Westall (1960b) has shown, however, that ASA can be converted into two anhydrides (denoted by B and C), a six-membered ring form, and a five-membered ring form, which can be separated by two-way chromatography, using phenol-ammonia-water and lutidine-water as the solvent systems. He has provisionally assigned the five-membered ring structure to that anhydride (Form C) which has an  $R_F$  value of 0.49 in phenol-ammonia-water. We have also been able to demonstrate three separate spots by using butanol-acetic acid-water and phenol-ammonia-water as the two solvent systems in two-way chromatography and have by this means shown that the second band  $R_F$  0.06 obtained by one-way chromatography using the former system, is anhydride B, and that anhydride C fails to separate from ASA in this solvent system.

Cerebrospinal fluid was also used undiluted and usually untreated, but sometimes treated as for plasma. The amino acids are extracted from plasma by passing 0.2-0.5 ml. through Amberlite 120 (H) in a column 7-8 cm. long containing approximately 0.4 g. resin. After washing well with water, the amino acids are eluted with 10 ml. 5 M. ammonium hydroxide. The eluate is taken to dryness *in vacuo* and the residue redissolved in 0.05 ml. water. Usually, 0.03 ml. was taken for chromatography. Two-way chromatograms of serum and spinal fluid are shown in Figs. 3 and 4 respectively.

**Isolation of Barium Arginino-succinate from Urine** (R. G. Westall, personal communication). The procedure

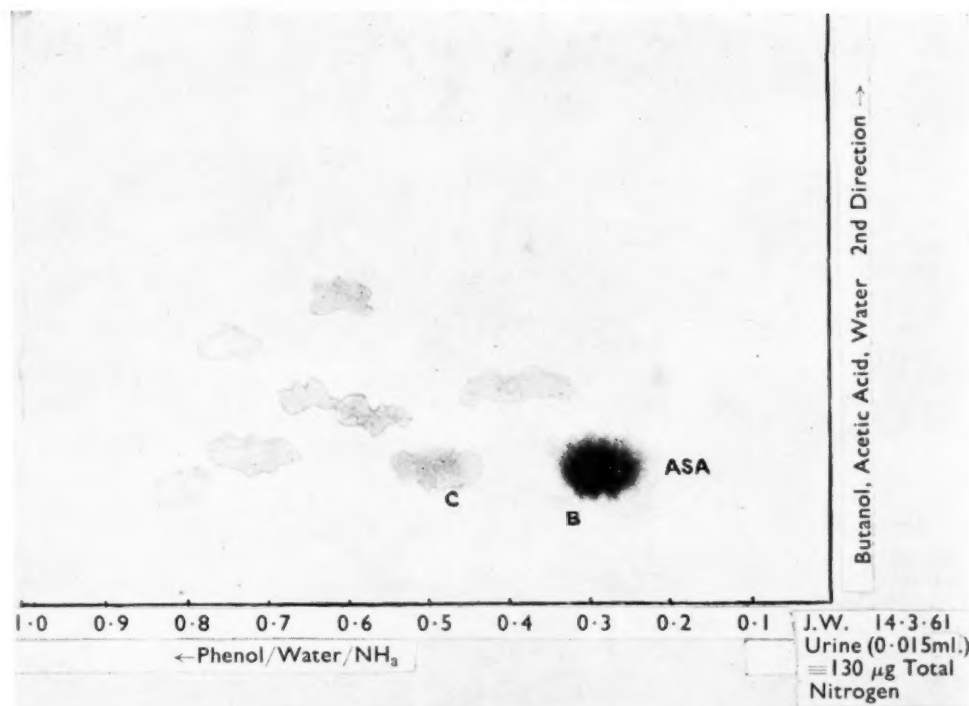


FIG. 2.—Two-way chromatogram of urine. The intense spot is the argininosuccinic acid (ASA). The two anhydrides (B and C) are indicated.

followed was similar to that used by Ratner *et al.* (1953) for isolating the acid after synthesis by an enzymatic method. Barium chloride solution (30 g. %, 9 ml.) was added to 100 ml. urine, followed by barium hydroxide (saturated solution, 20 ml.), and well mixed. The resulting mixture should be strongly alkaline. After standing at 4° C. overnight, the precipitate was separated either by filtration, using a Buchner funnel and Whatman No. 42 filter paper, or by centrifuging. To the clear filtrate was added three times its volume of absolute alcohol and the mixture was allowed to stand at 4° C. for 24 hours.

After decanting most of the supernatant and then centrifuging, the precipitate was redissolved in about 20 ml. water, centrifuged and reprecipitated with three times its volume of absolute alcohol. The final precipitate was washed first with 75% and then with 87% and finally with absolute alcohol, and then dried *in vacuo*.

For use as a standard in chromatography, an aqueous solution of the potassium salt was used. This was obtained by dissolving 0.25 g. of the pale yellow solid barium salt in 2.0 ml. warm water, adding 1.0 ml. of 1 M. potassium sulphate solution and finally centrifuging to remove precipitated barium sulphate and other insoluble material. The concentration was checked by estimation of the total and amino-nitrogen.

**Estimation of Argininosuccinic Acid in Urine, Cerebrospinal Fluid and Plasma.** Quantitative determinations

of the amino acid were usually performed on one-way rather than two-way chromatograms, using butanol-acetic acid-water or phenol-ammonia as the solvent systems. The paper chromatogram was stained with the cadmium acetate-ninhydrin reagent, as described above. The argininosuccinic acid segment was cut out, covered with 2 ml. methyl alcohol in a test-tube and allowed to stand for two to three hours. The alcohol was removed and the paper washed three times with 1 ml. amounts of methanol. The total eluate was centrifuged to remove debris and the final solution read in a cuvette at 509 m $\mu$  against a blank on the same paper. A normal solution of free argininosuccinic acid was used as a standard.

**Glutamine** was estimated in a similar way, using glutamine as a standard for comparison.

**Proof of Identity of the Amino Acid.** The unknown amino acid was identified first by a process of elimination and then by comparison with a specimen of known argininosuccinic acid. Known amino acids with similar  $R_F$  values in the same solvent systems were excluded by specific spot tests where applicable, e.g. cysteine and cystathionine. Phospho-ethanolamine was excluded by the failure to detect phosphorus in the eluate of the unknown spot. The only test on the paper giving a positive result was the Jaffé test, but the colour developed was weak compared with what might have been expected from the ninhydrin reaction. Proof of

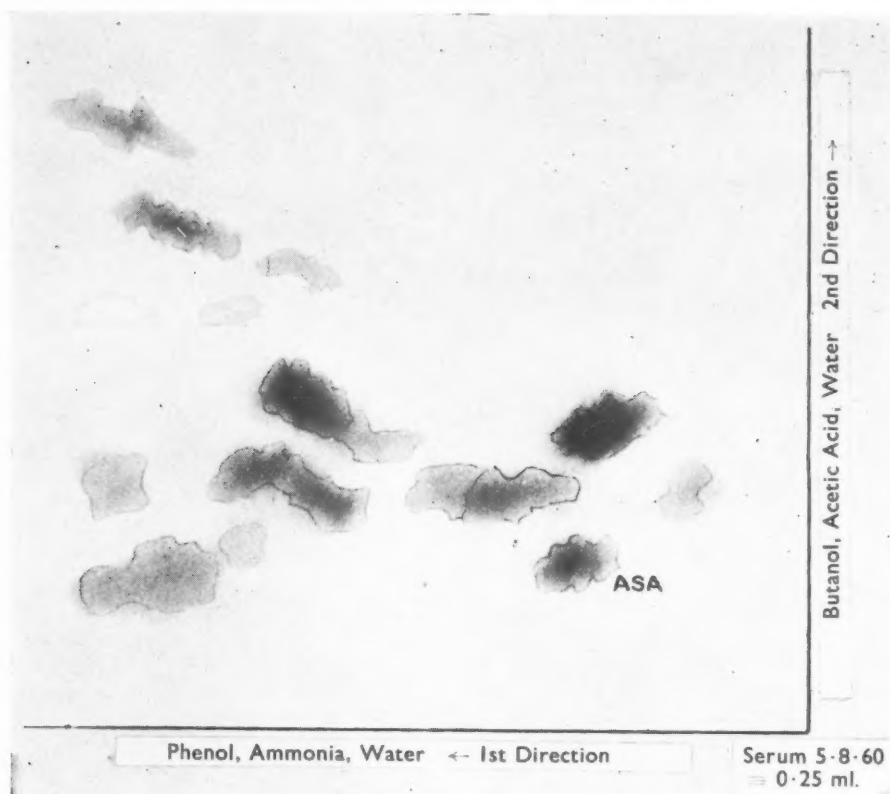
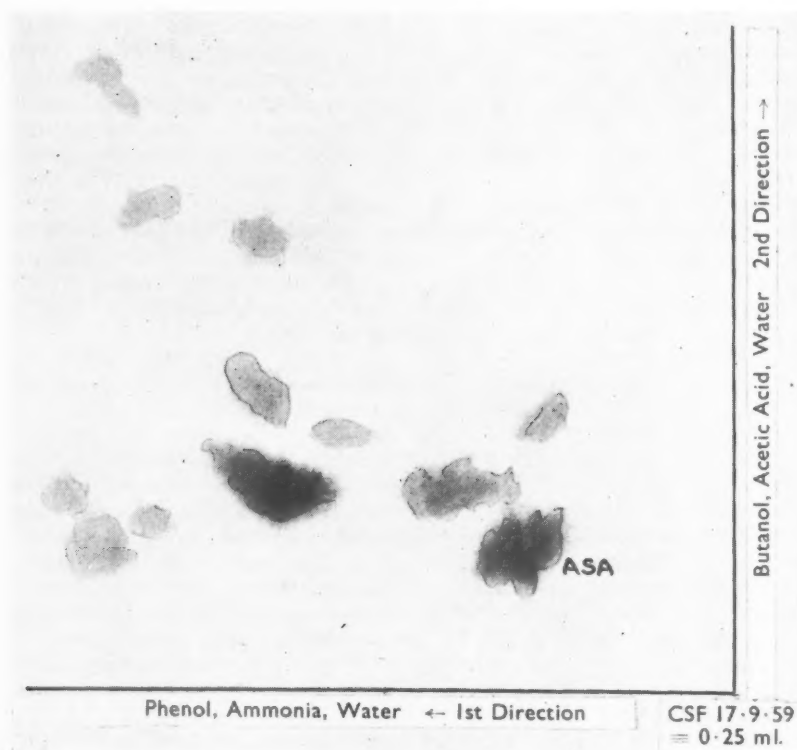


FIG. 3.



FIGS. 3 and 4.—Two-way chromatograms of serum and spinal fluid. In each case the spot lowest and to the right is argininosuccinic acid (ASA). Note that since identical amounts were taken in each case for chromatography, the relative intensities of the two spots give a measure of the relative amounts of the amino acid in the two fluids, with spinal fluid containing the larger amount.

FIG. 4.

identity with argininosuccinic acid rested also upon the following:

(a) The  $R_F$  value in phenol-ammonia-water was identical with that of argininosuccinic acid, and a mixture of the unknown with known acid gave only one spot after chromatography.

(b) Barium argininosuccinate was obtained in large yield from the patient's urine by the procedure described above.

(c) The solution of free argininosuccinic acid obtained by heating the aqueous solution of the barium salt with acid showed, on one-way chromatography, two ninhydrin positive bands, with  $R_F$  values corresponding to argininosuccinic acid and to its anhydride (Ratner *et al.*, 1953) and on two-way chromatography three bands, corresponding to the acid and its two anhydrides (Westall, 1960b).

**Argininosuccinic Acid Levels in Urine, Plasma and Cerebrospinal Fluid.** The method used suffered from the drawback that it was not always possible to isolate the required fraction completely. However, owing to the preponderant amount of the amino acid present, especially in urine, this did not constitute a serious error. In plasma, the error was minimized by using a normal plasma as blank, i.e. taking as blank value the ninhydrin fraction, having in normal plasma the same  $R_F$  value as argininosuccinic acid. No such difficulty arose with cerebrospinal fluid where the glutamine and argininosuccinic acid were the only preponderant spots, and the two have very different  $R_F$  values.

A number of 24-hour specimens of the urine were directly analysed for argininosuccinic acid, using known acid as standard. At other times a close approximation could be obtained by deducting urea nitrogen from total urinary nitrogen, allowing a further 10% of the total nitrogen for all other nitrogen-containing compounds usually present in urine and converting the residual nitrogen into weight of argininosuccinic acid. The range of excretion varied from 1.5 g. to 3.0 g. per 24 hours, according to diet. Although no other urinary amino acid was determined quantitatively, visual assessment of the stained chromatogram showed that there was no increase in the excretion of the other amino acids normally found.

The plasma level of argininosuccinic acid was estimated on several occasions, a typical value found being 4.4 mg. per 100 ml. The renal clearance calculated on a 24-hour specimen of the urine with a concentration of 0.28 g. per 100 ml. when the plasma level was 4.4 mg. per 100 ml. was 100 ml. per minute per 1.73 sq. metre, a value in good agreement with that found by Cusworth and Dent (1960). On the same occasion, the cerebrospinal fluid was found to be 9.5 mg. per 100 ml., a value more than twice that of the plasma, again agreeing well with those found by Cusworth and Dent (1960) in the original cases. It is also of interest to note that the level of glutamine in the cerebrospinal fluid was 8 mg. per 100 ml., i.e. within normal limits. Visual assessment showed that the plasma amino acid levels, other than argininosuccinic acid, were also within normal limits.

#### Effect of Protein and Amino Acid Intake on Argininosuccinic Acid Excretion

It has been shown (Ratner *et al.*, 1953) that argininosuccinic acid is an intermediate in the ornithine cycle, which it is generally believed is responsible for most, if not all, the urea synthesized in the body, with the liver as the main site of its production. It is reasonable to assume that in our patient argininosuccinic acid is implicated in the mental retardation. By analogy with phenylketonuria, rational therapy, as already stated, would involve a decrease in the formation of argininosuccinic acid and for this reason the effect of alteration in protein intake on its production as measured by excretion in the urine was investigated. The results are shown in Table 2.

A diet completely free from protein, but adequate in calories, resulted in a fall of argininosuccinic acid output from an initial level of 3.0 g. per day to about 0.6 g. per day (20% of initial level) by the seventh day. During the same period, urea excretion fell from 5.4 g. to 0.3 g. per day, i.e. 6% of initial level, a much greater fall than that of argininosuccinic acid. Whereas, on his normal diet, argininosuccinic acid nitrogen constituted less than 17% of the total urinary nitrogen, on the protein-free diet it constituted as much as 43%.

A comparable effect was observed when, in attempting to assess the effect of elimination of arginine from the diet, his normal feeds were replaced by a synthetic amino acid mixture, containing only the eight essential amino acids. The protein intake was only about 10 g. per day, very much less than on his normal feeds. Again, the daily excretion of argininosuccinic acid was considerably diminished compared with that on an ample protein intake and the ratio of argininosuccinic acid nitrogen to urea nitrogen and total nitrogen excreted were both greatly increased and were similar to those found when protein was completely eliminated from the diet.

When he was fed casein hydrolysate from which about half the arginine had been removed, again the protein intake (15 g. per day) was less than on his normal feeds. The total argininosuccinic acid excretion was a little higher than on his synthetic amino acid diet, although less than on his normal diet. The proportion of argininosuccinic acid nitrogen excretion to that of urea nitrogen or total nitrogen was less than on his synthetic amino acid feeds, and greater than that found when on normal diet. These results may be due to a combination of two effects, one due to the lowered protein intake, tending to raise the proportion of total nitrogen excreted as argininosuccinic acid and the other due to the lowered arginine intake, tending to lower the proportion of total nitrogen excreted as argininosuccinic acid.

The addition of, at first, 2 g. and afterwards 3 g. of arginine to his casein hydrolysate feeds, resulted in an increase of argininosuccinic acid excretion and in the proportion of argininosuccinic acid nitrogen to total nitrogen excretion (Table 2).

#### Discussion

In the ornithine cycle as modified by Ratner *et al.* (1953) and Ratner and Pappas (1949), citrulline

combines with aspartic acid by means of a condensing enzyme to form argininosuccinic acid and the cleavage of this substance to arginine and fumaric acid is reversibly catalysed by a splitting enzyme, argininosuccinase. The latter is present in mammalian liver, kidney and heart (Ratner *et al.*, 1953), and other organs, e.g. spleen, etc. (Walker, 1958), but the acid has not yet been found in plasma, cerebrospinal fluid or urine of man (Tomlinson and Westall, 1960), although presumably it must occur, if only transiently, in tissue cells. The presence in this patient of argininosuccinic acid in relatively high amounts suggests that the defect lies in an absence of the splitting enzyme, argininosuccinase.

That the deficiency is an inherited genetic disorder is suggested by the fact that in our case the anomaly was present at least 23 days after birth and also that the two previously reported cases (Allan *et al.*, 1958) were sibs. The level of urea in the blood was within normal limits and varied with protein intake, so that the capacity to synthesize urea was present. The amount of urea excreted was too great to be accounted for by its derivation solely from the arginine of the dietary or endogenous protein. For example, on one day during which the infant was on casein hydrolysate feeds, he excreted about 1.5 g. urea which, if it were all derived from arginine, would mean an intake of 4.3 g. arginine; he was actually receiving 0.39 g. arginine per day. It must be concluded, therefore, that most of the urea formed is derived from a urea cycle, presumably in the liver.

Allan *et al.* (1958) have suggested, on the basis of the higher levels of argininosuccinic acid in the cerebrospinal fluid compared with those in the plasma—a result which we also found in our case—that this metabolite is formed in the brain and diffuses into the cerebrospinal fluid; this suggestion received support from the recent work of Sporn, Dingman, Defalco and Davies (1959a, b and c) who showed that urea synthesis occurred in rat brain *in vitro*, contrary to the previous belief that urea was formed solely in the liver. Further, argininosuccinase has been found by Walker (1958) in the brain of the dog and by Ratner (private communication quoted by Tomlinson and Westall, 1960) in the brain of rats, steers and monkeys. This has also been demonstrated by Tomlinson and Westall (1960) who found evidence of enzyme activity in rat brain and other organs.

If the suggestion by Allan *et al.* (1958) is correct, it leads to the conclusion that there is an inherited enzyme deficiency present in the cells of one organ in the body, but not in another. It has been postulated (Landing, 1960), however, that in here-

ditary metabolic diseases the gene abnormality must be present in all cells in the body from birth and it is difficult to see how this could be reconciled with the foregoing conclusion. One possibility may be that the biosynthesis of urea in the liver in these cases is accomplished not by the ornithine cycle, but by another, normally little used. For example, Bach (1939) has presented some evidence that glutamic acid could take up ammonia to form glutamine which can combine with a further molecule of ammonia and carbon dioxide to yield glutamic acid and urea. Whether this is correct or not, it is not impossible that other cycles for urea synthesis exist in the body. On this supposition, argininosuccinic acid would be produced in our patient wherever the ornithine cycle should normally function, e.g. in the liver and in the brain. The lower argininosuccinic acid level in the blood compared with that in the cerebrospinal fluid would then be due to the rapid clearance of this substance by the kidney.

Another possibility is suggested by the fact that the cleavage of argininosuccinic acid is a reversible reaction and the reverse step may be necessary to provide argininosuccinic acid for other metabolic pathways (Ratner *et al.*, 1953) and it is the alternative pathway for argininosuccinic acid which is blocked, allowing the acid to accumulate.

The effect of variation in protein intake is interesting. As might be expected, when a protein-free diet was given, the excretion of argininosuccinic acid was considerably reduced, but not completely abolished and, in fact, it formed a considerably higher proportion of the total nitrogen excretion than when the patient was on a normal diet. That is, in protein deprivation, relatively more nitrogen is deviated to the synthesis of argininosuccinic acid than to the synthesis of urea, the amount of argininosuccinic acid nitrogen excreted falling not far short of that of urea nitrogen. If this is occurring in the brain, it suggests that this is a more essential cycle than that forming urea in the liver. It is interesting to note that during this time the liver diminished almost to normal size. This may have been due more to the lack of protein in the diet than to a restoration of the condition of the liver to normal.

Since ornithine and citrulline are not present in casein or in a normal diet, it was logical to attempt to reduce the formation of argininosuccinic acid by a reduction of arginine in the feeds, despite the fact that this acid is not the immediate precursor of ASA in the ornithine cycle. This was done as described above by oral feeds of a solution containing in suitable proportions the eight essential amino acids with additional glycine. Although

there was some reduction in the total amount of argininosuccinic acid excreted per day, this may have been largely due to the fact that the total protein intake was much less than on his normal feeds, similar to the effect found then on a protein-free diet. The liver this time was not reduced in size, in fact it became larger, suggesting that the reduction of ASA formation and excretion was not directly connected with the size of the liver. Again the child's condition deteriorated and did not improve until the amino acid feeds were withdrawn and normal feeding resumed.

Later, a casein hydrolysate mixture from which much of the arginine had been removed became available. On these feeds, daily ASA excretion started to rise above that on the mixture of synthetic amino acids, although less than when on a normal high protein diet. When arginine was added to the casein hydrolysate, ASA excretion was further increased, as was the proportion of ASA nitrogen excretion to total nitrogen excretion. Although Westall (1960b) concluded from his feeding experiments that restriction of arginine intake would not be of much value, our results point to a different conclusion. The different result in our patient is probably due to the relatively greater amount of arginine, 3 g. daily, added to his feeds which contained only 0.39 g. per day, whereas in Westall's patient, an 8-year-old boy, 2 g. arginine were added to a basic protein intake of 30 g. daily, containing about 1.2 g. arginine. However, some of our results are based on the analysis of the single day's excretion and must be assessed with caution as the differences are relatively small and there are, in any case, appreciable daily variations in the amounts of ASA excreted.

During this period of feeding, the child's liver altered little in size, again suggesting that there is little relation between ASA formation and the size of the liver. As on both previous occasions when he had been taken off his normal diet, on this occasion also, he became ill towards the end of the feeding experiment. The fall in plasma phosphorus level from 4.8 to 1.7 mg. per 100 ml. was almost certainly due to the continued low intake of phosphorus from the casein hydrolysate.

Microscopic examination of the hair revealed trichorrhexis nodosa, but whereas the breaks in the hair due to the more usual form of this condition fluoresce green with acridine orange, in our patient the fluorescence was red. An identical finding was present in the two original children with argininosuccinic aciduria (Allan *et al.*, 1958; Jarrett and Dent, personal communication). It is now obvious that the hair anomaly forms part of the condition

and is connected with the metabolic abnormality. Since arginine forms an important constituent of the hair keratin, it seems possible that the failure to form arginine from ASA leads to a deficiency of arginine with the formation of an abnormal hair keratin.

### Summary

An infant who had, in the first week of life, a sudden onset of severe illness with abdominal distension, gross liver enlargement, blood-stained vomiting and a period of unconsciousness, was found to be excreting large amounts of argininosuccinic acid (ASA), an intermediate compound in the biosynthesis of urea. His subsequent history has been of mental and physical retardation, persistent liver enlargement, skin lesions and episodes of convulsions, or loss of consciousness. The clinical features of the present case are compared with those of the two previously reported cases in one family (Allan *et al.*, 1958). An identical hair anomaly was found in all three cases.

The level of ASA in the cerebrospinal fluid was higher than that in the plasma, whilst the blood urea was normal. Reduction of protein intake apparently resulted in the reduction of ASA formation, and addition of arginine to the feeds gave increased ASA excretion. Although the accumulation of ASA in the cerebrospinal fluid and a blood urea within the normal range might be explained by a genetic deficiency of argininosuccinase in the urea cycle in the brain, this postulate would necessitate a genetic defect in the cells of only one organ, other cells being normal. It is therefore suggested that in these cases urea is synthesized in the liver by a cycle other than the normal one involving ASA or, alternatively, ASA accumulates because of a defect in metabolic pathways other than the biosynthesis of urea.

We are very much indebted to Dr. R. J. K. Brown for permission to continue our studies on this patient, now under his care, and for his helpful comments. We also record our thanks to Dr. Winifred Young for help and advice in the treatment of some of the severe episodes of illness, and to Dr. Thea Rose for her assistance in the earlier investigations. The unfailing help and co-operation of the nursing staff, in particular Sister Dresdner, is also gratefully acknowledged.

Messrs. Allen and Hanburys, Ltd., kindly provided the low arginine-casein hydrolysate preparation used.

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# LOW BIRTH WEIGHT DWARFISM

BY

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'Every third man a pigmy!—some by rickety heads and hump backs; others by bandy legs; a third set arrested by the hand of Nature in the sixth and seventh years of their growth; a fourth in their perfect and natural state like dwarf apple-trees; from the first rudiments and stamina of their existence, never meant to grow higher.' Lawrence Sterne, *A Sentimental Journey*.

In the course of time a variety of names have been given to Sterne's 'dwarf apple-trees': primordial dwarfism (von Hansemann, 1902), ateliosis (Gilford, 1904, 1911), microsomie essentielle (Lévi, 1910), nannosomia (or nanosomia) vera, constitutional, proportionate, genetic, and intra-uterine (Russell, 1954) dwarfism. Recently Seckel (1960) has shown that a distinct variety of low birth weight dwarfism exists, which he has called, using Virchow's (1892) original term, 'bird-headed'. All these terms appear to refer to a disorder of growth by implication present at or before birth, in which the individual is of extremely small stature, but otherwise exhibits no recognizably causative disease. For the purposes of this paper the name 'Low Birth Weight Dwarfism' is used to cover all the terms mentioned above.

It is surprising that the birth weights of such cases have received so little attention. Troen and Blumberg (1948) did, however, make a brief study of 40 cases of dwarfism and showed that their mean birth weight was significantly lower than that of normal individuals. Apart from this paper, in which many essential clinical details are lacking, there is little definite information in the literature. The continued use of eponymous terms based upon the early descriptions of dwarfism and infantilism has blurred the differences between hypopituitary dwarfism and low birth weight dwarfism. The condition described by Lorain (1871) and subsequently by Lévi (1908) appears to have been secondary to tuberculosis (Lorain), while Lévi's cases probably suffered from congenital syphilis

and a cardiac lesion respectively. A secondary hypopituitarism might result from such chronic conditions, but the clinical picture is different from what we now understand as hypopituitary dwarfism. Similarly, Brissaud's (1897) cases of 'infantilisme myxoedemateux' would now be considered as juvenile myxoedema, though a similar clinical condition may result from a general hypopituitary state (Spence, 1953).

Nevertheless, Lévi (1910) gave a clear description of 'microsomie essentielle' in two families in which a dominant mode of inheritance was operative. Similar pedigrees were also reported by Gilford (1904, 1911). Gilford used the term 'ateliosis' which he divided into 'sexual' and 'asexual' forms according to the presence or absence of normal sexual maturity. He suggested that the growth defect in 'sexual ateliosis' was present from birth (low birth weight dwarfism): the asexual type appears to be equivalent to hypopituitary dwarfism in modern terminology.

In 1912 Rischbieth and Barrington made an extensive study of the genetic aspects of dwarfism using the term 'ateliosis' but without differentiating between Gilford's two types. Rössle (1924), in a comprehensive survey of growth and its disorders, produced the classification which is still in common use. He considered that 'primordial dwarfism' was distinct from all other forms of dwarfism and that the condition was always present at birth. The suggestion that low birth weight dwarfism might be due to some intra-uterine disturbance was made independently by Silver, Kiyasu, George and Deamer (1953), Russell (1954) and Silver (1959).

It is the purpose of this paper to present three cases of low birth weight dwarfism and to discuss with reference to these cases and to the literature the various clinical types which can now be distinguished.

## Case Reports

**Case 1** (Figs. 1 and 3 and Table 1). The first child of healthy parents, she was born on May 8, 1947, by breech

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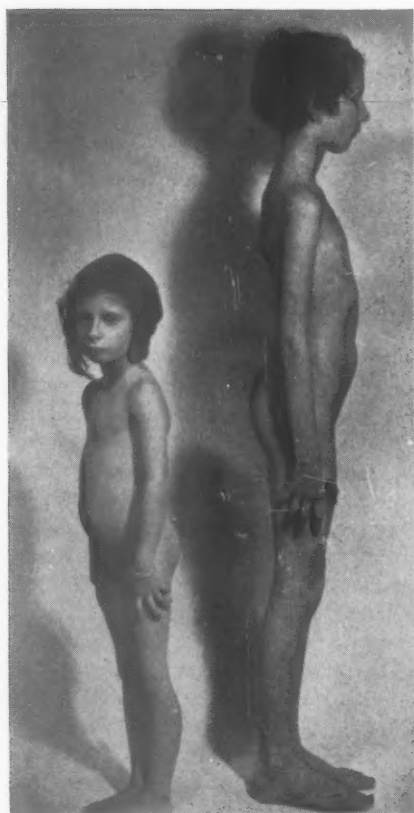


FIG. 1.—Bird-headed dwarfism: Case 1 with normal control of the same age (8 years 9 months).

delivery, weighing 4 lb. 4 oz. (1.93 kg.) after a pregnancy lasting 40 weeks. The pregnancy was normal apart from the fact that the mother thought that her abdomen had been small in proportion to the length of her pregnancy. The neonatal period was uneventful.

Her weight gain was always slow; by the age of 3 years she only weighed 15 lb. (6.82 kg.), at the age of 5½ years her weight was 20 lb. (9.26 kg.) and her height 35 in. (87.6 cm.), and at 6 years her weight was 27 lb. 1 oz. (12.27 kg.) and height 36½ in. (91.4 cm.). Her appetite was always considered to be poor. She was treated for long periods with pituitary extract by mouth without apparent effect.

There was no family history of dwarfism, but the height of the mother was 5 ft. 2 in. (157.5 cm.) and of the father 5 ft. 4 in. (162.6 cm.). The age of the mother at the birth of this first child was 23 years and that of the father 29 years. There were no other children apart from the two girls described later in this paper.

At the age of 8 years and 9 months she was a small slender shy child, with a slight squint, due to hypermetropia, for which she wore glasses. Her face was small with a narrow beaky nose and small receding chin.

No treatment was given and on her return home she continued to make satisfactory progress at school. She

was seen again at the age of 12 years and 4 months; during this period she had gained 6 in. (15.2 cm.) in height and 14 lb. (6.37 kg.) in weight. Her bodily proportions were unchanged and her head circumference had only increased by 0.5 in. (1.25 cm.). At this last examination pubic hair was present but there was no other evidence of puberty.

TABLE 1

Measurements	First Attendance	Second Attendance
Chronological age ..	8 years 9 months	12 years 4 months
Skeletal age* (years) ..	7	9
Height age (years) ..	4	6
Height (cm.) ..	99.1	114.3
Weight (kg.) ..	11.92	18.29
Head circumference (cm.) ..	45.7	46.9
Chest circumference (cm.) ..	45.7	49.5
Span (cm.) ..	96.5	110.5
Upper measurement† (cm.) ..	53.3	58.4
Lower measurement† (cm.) ..	48.3	55.9

\* Vogt and Vickers (1938).

† Using symphysis pubis as middle fixed point.

*Investigations.* The following investigations were carried out at 8 years 9 months unless otherwise stated.

**BLOOD CHEMISTRY.** Non-protein nitrogen, 33.8 mg. per 100 ml.; plasma chloride, 104 mEq. per litre; plasma CO<sub>2</sub>, 26 mEq. per litre; blood inorganic phosphorus, 4.6 mg. per 100 ml.; serum calcium, 11.6 mg. per 100 ml.; plasma alkaline phosphatase, 11 units per 100 ml. (King-Armstrong); whole blood cholesterol, 84 mg. per 100 ml. (normal by this method at 8 years, 90-120, and at 4 years 80-100 mg. per 100 ml. (Dutton, 1932)).

**GLUCOSE TOLERANCE TEST** (12 g. glucose orally). Fasting, 92 mg. per 100 ml.; after half an hour, 160 mg. per 100 ml.; after one hour, 164 mg. per 100 ml.; after one and a half hours, 80 mg. per 100 ml.; after two hours, 56 mg. per 100 ml.; after two and a half hours, 70 mg. per 100 ml.; and after three hours, 84 mg. per 100 ml.

**URINE.** Routine examination showed no abnormality; sugar chromatography revealed no abnormal sugars; amino nitrogen per 24 hours was 69 mg. (Van Slyke ninhydrin method), normal for weight, 26 mg. or 1 mg. per lb. per day; 17-ketosteroids, 0.90 mg. per 24 hours (Tompsett, 1949).

**MANTOUX.** 1:5,000 negative. Toxoplasmosis dye test was negative and complement fixation test negative.

**RADIOLOGY.** The assessments of skeletal age are according to Vogt and Vickers (1938).

At the age of 8 years and 9 months the bones were slender and small; there was narrowing of both femoral necks, and bilateral rudimentary cervical ribs. The skull was small and pituitary fossa normal. The skeletal age was 7 years.

At the age of 12 years and 4 months there was narrowing of both femoral necks; the skeletal age was 9 years.

**PSYCHOLOGICAL REPORT.** This was carried out at the age of 8 years and 9 months. She was tested on the Terman-Merrill (form L) scale and on the Goodenough 'Draw-a-man' test. In the former, her mental age was given as 6 years (I.Q. 74), but this was considered to be

a considerable underestimate as her performance seemed to be inhibited by lack of confidence. The Goodenough test gave a mental age of 8 to 9 years.

**Comment.** This child was of very slender build with a bird-like face. There was no abnormality of her blood chemistry, but her glucose tolerance curve showed a moderate reactive hypoglycaemia. Estimation of her 17-ketosteroid output gave a value perhaps more in conformity with her 'height age' rather than her chronological age. Her daily output of amino acids was higher than would have been expected on a weight basis, but this may be related to a greater turn-over of amino acids than would have been expected for the actual weight, a problem which was discussed in part by Ranke and von Voit (1886). The skeletal age was markedly delayed at both examinations, but apart from this there was no evidence of hypopituitarism. The appearance of pubic hair at the age of 12 years and 4 months is against hypopituitarism, though at this time there was no breast development. Psychological testing at 8 years and 9 months showed social immaturity rather than intellectual inadequacy.

**Case 2** (Figs. 2 and 3 and Table 2). This child, the sister of Case 1, was born on February 22, 1949, by breech delivery at full term, weighing 3 lb. 2 oz. (1.42 kg.). The pregnancy had been uneventful, though the mother had noticed that she was 'small' all through her pregnancy. At birth she was 'slow to cry', but was not cyanosed and did not become jaundiced. By the age of 8½ weeks she weighed 5 lb. (2.27 kg.) and at 1 year 10 lb. (4.54 kg.); she sat up at 1 year, walked at 1 year 3 months and spoke at 2 years. She was treated for a short period with whole pituitary gland orally without effect.

She was admitted to the Royal Hospital for Sick Children with her sister on February 22, 1956, for investigation.

She had a similar facial appearance to her sister and was of very slender build.

TABLE 2

Measurements	First Attendance	Second Attendance
Chronological age (years) ..	7	10
Skeletal age* (years) ..	4.5	7
Height age (years) ..	3	5
Height (cm.) ..	92.7	107.9
Weight (kg.) ..	10.00	14.49
Head circumference (cm.) ..	44.4	45.2
Chest circumference (cm.) ..	43.2	45.7
Span (cm.) ..	87.6	104.1
Upper measurement† (cm.) ..	48.3	54.6
Lower measurement† (cm.) ..	44.4	53.3

\* Vogt and Vickers (1938).

† Using symphysis pubis as middle fixed point.

**Investigations.** The following investigations were carried out at the age of 7 years unless otherwise stated.

**BLOOD CHEMISTRY.** Non-protein nitrogen, 37.5 mg. per 100 ml.; plasma chloride, 102 mEq. per litre; plasma  $\text{CO}_2$ , 25 mEq. per litre; blood inorganic phosphorus,



FIG. 2.—Bird-headed dwarfism: Case 2 with normal control of the same age (7 years).

4.7 mg. per 100 ml.; serum calcium, 11.2 mg. per 100 ml.; plasma alkaline phosphatase, 10 units per 100 ml. (King-Armstrong); whole blood cholesterol, 75 mg. per 100 ml. (normal at 7 years, 70-100; and at 3 years, 60-90 mg. per 100 ml. (Dutton, 1932)).

**GLUCOSE TOLERANCE TEST** (12 g. of glucose given). Fasting, 42 mg. per 100 ml. (no symptoms); after half an hour, 135 mg. per 100 ml.; after one hour, 88 mg. per 100 ml.; after one and a half hours, 58 mg. per 100 ml.; after two hours, 23 mg. per 100 ml. (no symptoms).

A repeat test (12 g. of glucose) gave the following results: Fasting, 68 mg. per 100 ml.; after half an hour, 72 mg. per 100 ml.; after one hour, 106 mg. per 100 ml.; after one and a half hours, 56 mg. per 100 ml.; after two hours, 48 mg. per 100 ml.; after two and a half hours, 58 mg. per 100 ml.; and after three hours, 44 mg. per 100 ml.

**URINE.** Routine examination showed no abnormality; sugar chromatography revealed no abnormal sugars; amino acid nitrogen output per 24 hours was 83 mg. (raised) (Van Slyke ninhydrin method); 17-ketosteroids, 0.61 mg. per 24 hours (Tompsett, 1949); a level more in keeping with her 'height age' than her chronological age.

**MANTOUX.** 1:5,000 negative. Toxoplasmosis dye test was negative and complement fixation test negative.

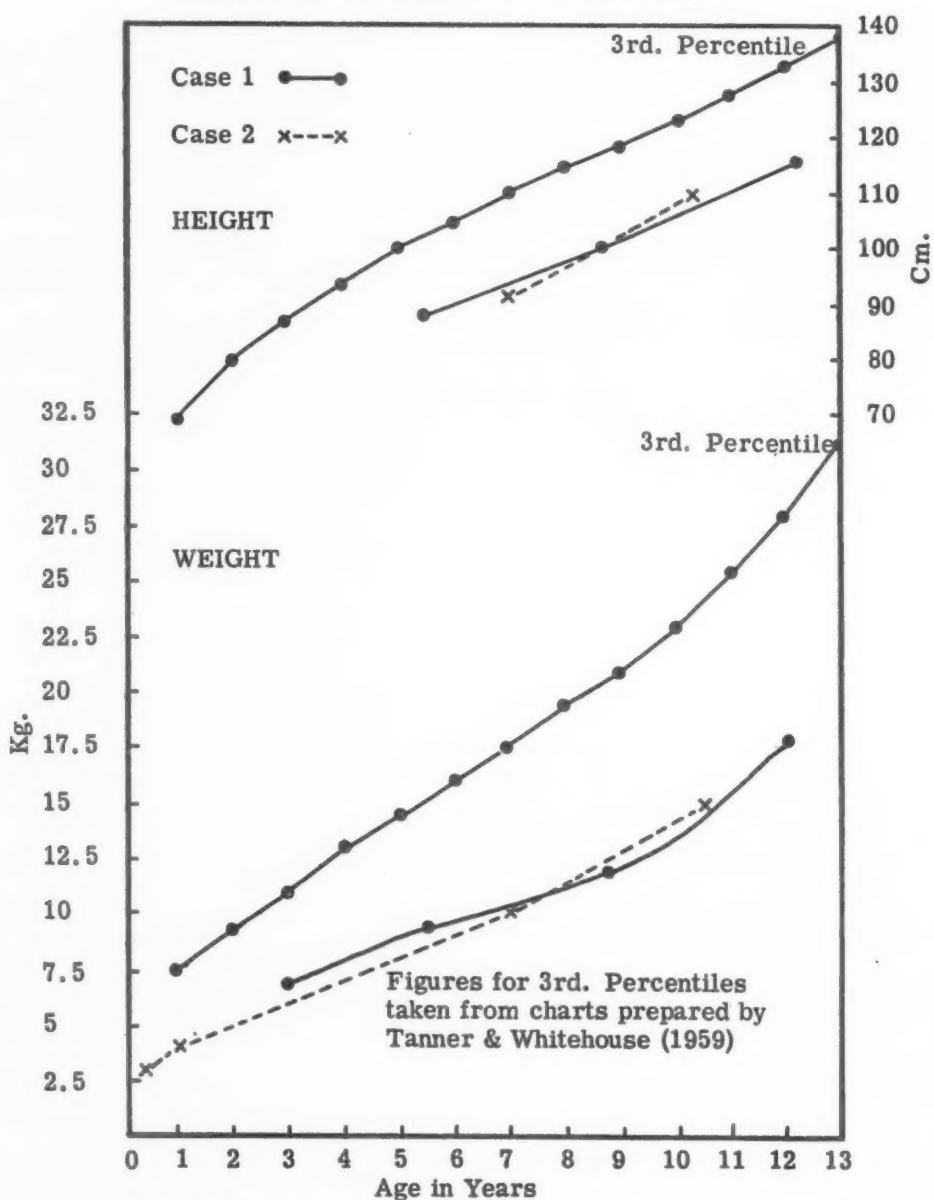


FIG. 3.—Progress in height and weight of Cases 1 and 2 in relation to 3rd percentile.

**RADIOLOGY.** The assessments of skeletal age are according to Vogt and Vickers (1938). At the age of 7 years the skull was small and pituitary fossa normal. At the age of 10 years and 6 months there was narrowing of both femoral necks (Fig. 4). The skeletal age was 7 years.

**PSYCHOLOGICAL REPORT.** Psychological testing was carried out at the age of 7 years. She was tested on the Terman-Merrill form L and Goodenough 'Draw-a-man' test. On the former she had an I.Q. of 79, but the Goodenough test gave a mental age of 6 to 9 years.

There was evidence of lack of confidence inhibiting her performance.

*Comment.* This child was strikingly similar to her sister in every way except for a low fasting blood sugar and extreme reactive hypoglycaemia in her first tolerance curve.

**Case 3** (Fig. 5 and Table 3). This girl (M.C.), the first-born of twins, was delivered 4½ weeks before term on December 14, 1957, weighing 3 lb. 1 oz. (1.39 kg.). The

TABLE 3

Measurements	Case 3 (M.C.)	Normal Twin (H.C.)
Chronological age (years) ..	1.5	1.5
Skeletal age* (months) ..	3-6	18
Height age (months) ..	3	24
Height (cm.) ..	61.0	82.5 (between 75th and 90th percentile)
Weight (kg.) ..	4.95	10.40
Head circumference (cm.) ..	44.5	46.0
Chest circumference (cm.) ..	38.0	50.0
Span (cm.) ..	62.0	85.5
Upper measurement† (cm.) ..	39.0	46.0
Lower measurement† (cm.) ..	22.0	36.5

\* Vogt and Vickers (1938).

† Using symphysis pubis as middle fixed point.

delivery of the second twin was obstructed by the placenta of the first which had partly separated and was protruding through the os. The second twin, who weighed 5 lb. 13½ oz. (2.66 kg.), was extracted as a breech under general anaesthesia. The first placenta was 'infarcted' with a velamentous insertion, but the second placenta appeared to be normal. The placentae were quite separate, though the chorions were united; the twins were considered to be binovular. There were five other living children born before the twins, all of normal birth weight. One child, born in 1947, birth weight 6 lb. 4 oz. (2.74 kg.), died of 'convulsions' at the age of 3 months, and in 1951 there was a miscarriage at 3½ months gestation.

*Progress.* M.C. appeared active at birth while the second twin (H.C.) was said to be 'slightly shocked', but subsequently progressed quite normally. M.C., however, gained weight slowly and was discharged from hospital after 10 weeks, weighing 5 lb. 7 oz. (2.47 kg.).

By the age of 4 months H.C. weighed 12 lb. 6 oz. (5.63 kg.), while M.C. had only gained 3 oz. (0.085 kg.) since her discharge from the maternity hospital. She was therefore admitted to hospital for investigation. She remained in hospital for eight weeks, gaining weight slowly up to 7 lb. 3 oz. (3.27 kg.). The only abnormalities detected were slightly raised blood urea and a faint systolic murmur audible down the left side of the sternum, but at the age of 10 months the murmur was no longer audible (for investigations, see below). At the age of 1 year she was again admitted to hospital with the diagnosis of pneumonia.

She was finally admitted to the Royal Hospital for Sick Children, Glasgow, at the age of 1½ years for further investigation.

*Development.* She sat up at 8 months and crawled at 1 year. At 1 year and 4 months she was able to stand with support. At the age of 1½ years, though she appeared alert and active, she was unable to speak at all, though she made babbling and imitative noises.

*Investigations.* The following investigations were carried out at first admission when she was 4 months.



FIG. 4.—Radiograph of hips of Case 2, showing narrowing of femoral necks.



FIG. 5.—Dwarfed twin: Case 3 with normal twin at the age of 18 months.

The blood urea was 53 mg. per 100 ml.

The urine was normal to routine testing. Chromatography revealed a normal amino acid pattern, and glucose and xylose were present in normal amounts.

The stool had no pathogens on culture. Microscopy showed no abnormal constituents. Tryptic digestion was up to a dilution of 1:6,000.

A radiograph of the chest revealed increased bronchovascular markings in right upper lobe; there was no abnormality of the abdomen, and no abnormality of the wrist apart from the absence of the centres of capitate and hamate bones.

On her second admission at the age of 1 year further investigations were undertaken.

A full blood count was normal; the cerebrospinal fluid revealed 2 cells per c.mm.; protein, 30 mg. per 100 ml.; chloride, 128 mEq. per litre, and sugar, 46 mg. per 100 ml.

Radiographs of the chest and skull were normal; there were no centres for capitate and hamate bones in the wrist.

She was admitted for the third time at the age of 18 months.

**BLOOD CHEMISTRY.** Serum sodium, 145 mEq. per litre; serum potassium, 5.6 mEq. per litre; plasma chloride, 100 mEq. per litre; plasma  $\text{CO}_2$ , 22 mEq. per litre; calcium, 11.2 mg. per 100 ml.; blood urea, 55 mg. per 100 ml., and serum cholesterol, 370 mg. per 100 ml. (normal 150-200 mg. per 100 ml. (MacIntyre and Ralston, 1954)).

**GLUCOSE TOLERANCE TEST** (5 g. glucose given). Fasting, 49 mg. per 100 ml.; after half an hour, 87 mg. per 100 ml.; after one hour, 91 mg. per 100 ml.; after one and a half hours, 56 mg. per 100 ml.; after two hours, 59 mg. per 100 ml.; and after two and a half hours, 67 mg. per 100 ml.

**URINE.** 17-ketosteroids per 24 hours were 0.33 mg. and 0.35 mg. on two successive days (Tompsett, 1949). This is within the normal for her 'height age' or her chronological age.

**RADIOLOGY.** The long bones were small and there was some osteoporosis, with thin cortex and deficient trabeculation. Skull and pituitary fossa were normal, skeletal age between 3 and 6 months. Assessment of skeletal age was according to Vogt and Vickers (1938).

Comparison with other twin revealed the following:

	M.C.	H.C.
Blood group:	A. Rh negative	AB. Rh negative
Eye colour:	Blue	Light brown
Hair colour:	Light reddish	Dark reddish

**Comment.** The main clinical features of this child were her very low intelligence and her extreme degree of dwarfing, which was even more marked than in Cases 1 and 2. In this child the rather flat glucose tolerance curve suggested adrenal insufficiency, perhaps secondary to hypopituitarism, and this was confirmed by the very retarded skeletal development; the high blood urea was an unusual feature and remains unexplained, in the absence of any demonstrable renal lesion or electrolyte disturbance.

In general, the findings were similar to the case, also a twin, described by LoPresti, St. Martin and Pascual (1952).

### Discussion

**Definition.** Though a low birth weight is essential for the diagnosis of this condition, a definition by length would be preferable. However, the length at birth is not always measured and is seldom recollected by parents. It is necessary to take into account the fact that many infants, fully mature by dates, weigh less than 5½ lb. (2.50 kg.), but Drillien (1957) has shown that very few of these weigh less than 4½ lb. (2.05 kg.). A full-term baby weighing less than 4½ lb. may therefore be considered to be abnormally small. Estimations of the length of pregnancy are accepted to be inaccurate by about two weeks in either direction and it therefore seems reasonable to include as mature infants born at or after 38 weeks. There is also the possibility that low birth weight itself, irrespective of the length of pregnancy, might produce permanent dwarfism, but Drillien (1958) has shown that though premature babies of very low birth weight (i.e. 3 lb. (1.36 kg.) or less) seldom attain the mean values for height and weight by the age of 9 years (which was the oldest group in Drillien's series), only a few fall below the 3rd percentile and would be considered as dwarfed. Similar results were obtained in a follow-up of very small prematures by Dann, Levine and New (1958). Not all low birth weight dwarfs are necessarily born at term; M.C. (Case 3, birth weight 3 lb. 1 oz. (1.39 kg.)) one of twins, was born at 35½ weeks, but the other twin, who weighed 5 lb. 13½ oz. (2.66 kg.) can fairly be considered as an adequate control.

The following diagnostic criteria must therefore be fulfilled before accepting a diagnosis of low birth weight dwarfism with the qualifications mentioned above.

- (1) Birth weight of less than 4½ lb. (2.05 kg.).
- (2) Length of gestation of not less than 38 weeks (with the qualification for twins mentioned above).
- (3) Height below the 3rd percentile throughout period of observation.
- (4) No gross physical disproportion.

**Clinical Types.** Much of the literature on dwarfism has been concerned with rather sterile discussions about the existence or non-existence of 'miniature' individuals with bodily proportions identical with those of a normal person of the same age. In practice most comparisons have been made by means of the 'height-age' or 'konstitutionelle Alter'

TABLE 4  
CLASSIFICATION OF LOW BIRTH WEIGHT DWARFISM

	Type				
	Bird-headed	Snub-nosed		Russell-Silver	Dwarfed Twin
Aetiology .. ..	? Recessive ? Environmental	Dominant	Recessive	Environmental	? Environmental ? Hypopituitarism
Pregnancy .. ..	Normal	Normal	Normal	Early haemorrhage	Twin pregnancy; other twin normal
Associated abnormalities	Minor skeletal	Incomplete descent of testes	None	Body asymmetry minor skeletal	None
Body build .. ..	Slender	Stocky	Stocky	Slender	Normal
Intelligence .. ..	Low or low normal	Normal	Normal or low	Normal	Very low
Sexual development .. ..	? Delayed	Normal	Normal	? ?	? ?
Skeletal age .. ..	Delayed	Normal	Normal	Delayed	Delayed
Reference case .. ..	Cases 1 and 2 (Figs. 1 and 2)	Cases 4 and 5 (Figs. 6 and 7)	Case 6 (Figs. 8 and 9)	Case 7 (Fig. 10)	Cases 3 and 8 (Fig. 5)
Author .. ..	(1) Seckel (1960) (2) This article for Cases 1 and 2	Lévi (1910)	von Verschuer and Conradi (1938)	(1) Silver (1959); Silver <i>et al.</i> 1953 (2) Russell (1954) (3) This article for Case 7	(1) LoPresti <i>et al.</i> (1952) for Case 8 (2) This article for Case 3

(Kirchhoff, Lehmann and Schaefer, 1954), a method in which the dwarf's measurements are compared with those of a normal child with the same height as the dwarf. As ordinarily used, this method has the considerable disadvantage that the 'standard' child does not have the same proportions as a dwarf of the same height but many years older. In order to avoid this difficulty various ratios have been proposed (head circumference : height, arm span : height, upper measurement : lower measurement, etc.) which may have statistical validity when comparing one large group with another. But when such ratios are applied to individuals it is found that the standard deviations of the component measurements are great enough to cause considerable variations in the supposedly constant ratios. Another difficulty in the use of sets of standard ratios is the fact that small errors in both measurements may produce a large error in the ratio.

From a clinical point of view the object is to obtain such information from body measurements as will help one to place a dwarf in a particular category within a general classification. For this purpose the only reliable form of comparison is still the 'height-age' method, using only measurements whose standard deviations from the mean are known. In practice this allows the use of the height as determining the appropriate 'height-age' standard, and the head circumference and arm span for comparison. There appear to be no data for the standard deviations from the means for upper and lower measurements, and the weight and chest circumference are likely to be invalidated by variations in body fat. It remains, therefore, to see whether the deviations from the mean values of head circumference and arm span show any consistent trends

in the four types of low birth weight dwarfism considered here (Tables 4 and 5).

*I. Low Birth Weight Dwarfism: Bird-headed Type* (Cases 1 and 2; Figs. 1 and 2). Seckel has shown that the bird-headed dwarfs have a characteristic beaky nose and receding jaw. They are of very slender build. Their intelligence is low or low normal and appears to decline as they get older; possibly this is related to the small absolute size of their skulls, another characteristic feature. Skeletal development tends to be retarded, more so in the regions where there are congenital abnormalities of the bones. At present it is not possible to say whether sexual development proceeds normally or is delayed.

Seckel considers that bird-headed dwarfism is inherited as a recessive, but the documentation of many of the older cases in the literature is incomplete. It may, however, be significant that in Seckel's Case 1 the paternal grandparents were first cousins.

In the two cases described here, the face and clinical features fit well with Seckel's description. The occurrence of two cases in one sibship is very suggestive of a recessively inherited disorder, particularly in view of the small stature of the parents, but a recurring abnormality of the intra-uterine environment cannot be excluded. In both cases there was a curious narrowing of the femoral necks (Fig. 4) and in Case 1 bilateral cervical ribs were present. The appearance of pubic hair in Case 1 at the age of 12 years, without other evidence of puberty cannot be taken to indicate any specific endocrine condition, as this may occur in normal girls and also in ovarian agenesis (Wilkins, 1957).

Case no.	Bird-headed		
	1*	2*	4†
Sex	Female	Female	Male
Birth weight (kg.)	1.93	1.42	Low
Age at examination	12 years 4 months	10 years 6 months	50 years
Height (cm.)	114	108	106
Height age	6 years	5 years	5 years
Skeletal age	9 years	7 years	Normal
Head circumference (cm.)	47	45	50
Mean for height age (cm.)	51.25 (−2 S.D.: 48.17)	50.50 (−2 S.D.: 47.82)	51.15 (−2 S.D.: 48.17)
Mean for actual age (cm.)	53.33 (−2 S.D.: 50.77)	52.23 (−2 S.D.: 49.47)	56.62† (−2 S.D.: 53.82)
Arm span (cm.)	110	104	—
Mean for height age (cm.)	113.7 (−2 S.D.: 100.38)	107.6 (−2 S.D.: 96.92)	—
Reference	This paper	This paper	Lévi (1910)

\* Cases 1 and 2: sisters.

† Cases 4 and 5: father and son.

‡ Mean values for 17½ years.

§ Values from Falkner (1958) extrapolated when necessary; all others are from Lévi (1910).

From the clinical features described above and from the various investigations performed on Cases 1 and 2, it seems unlikely that hypopituitarism is the cause of the growth lag. The facial appearance

makes the head look unduly small, but Seckel has concluded that the head circumference is reduced in the same proportion as the height. From Table 5 it can be seen that in Cases 1 and 2 the head circumference is smaller than −2 S.D. from the mean for the height-age standard, and this seems to be characteristic of bird-headed dwarfism. The reduction in arm span, compared to the height-age standard is, however, probably not significant.

*II. Low Birth Weight Dwarfism: Snub-nosed Type* (Cases 4, 5 and 6; Figs 6, 7, 8 and 9; for summary of case histories see appendix). There is at present no satisfactory term to describe these dwarfs: 'snub-nosed' is not really accurate as it is the bridge of the nose which is flat, while the tip is normal. The typical appearance is well shown in Figs. 6 and 8.

In this type of dwarfism the general appearance is stocky, the intelligence is normal in the dominant type and sometimes low in the recessive type. Sexual maturation occurs at the normal age or may be slightly delayed and skeletal abnormalities are absent. Partially (Case 4) or completely (Case 5) undescended testes seem to be relatively common. In most of the families described a dominant mode of transmission is found (Gilford, 1904, 1911; Lévi, 1910; Rössle, 1924), but in 1938 von Verschuer and Conradi described a family in which six snub-nosed dwarfs (three males and three females) occurred in three sibships in three generations, with consanguinity in the parentage of one of the sibships (maternal great grandfather and paternal grandfather were brothers).

This type of dwarfism has been termed 'normocephalic', but in the three cases (Cases 4, 5 and 6) quoted here, the head circumference was less than



FIG. 6.—Snub-nosed dwarfism; dominant type: Cases 4 and 5 from Lévi (1910).

OF C. SES TO HEIGHT-AGE STANDARDS

Sub-nosed Types		Russell-Silver		Dwarfed Twin	
4†	5†	Recessive	7	3	8
Male Low 50 years 106 5 years Normal 50	Male Low years 6 months 77 15 months Normal 46	Female Low 36 years 125 8 years 6 months Normal 49.6	Male 1.37 5 years 7 months 94 3 years§ 3-5 years 50.5	Female 1.39 (35½ weeks) 1 year 6 months 60 3 months§ 3-6 months 45	Female 1.31 1 year 9 months 55 2 months§ 'Delayed' 43
(-2 S.D.: 45.00) (-2 S.D.: 52.13)	(-2 S.D.: 45.00) (-2 S.D.: 52.13)	51.52 (-2 S.D.: 49.06) 54.85 (-2 S.D.: 53.09)	50.48 (+2 S.D.: 53.0) 51.15 (-2 S.D.: 49.31)	39.78 (+2 S.D.: 41.9) 47.0 (-2 S.D.: 44.8)	37.98 (+2 S.D.: 40.1) 47.45 (-2 S.D.: 45.25)
---	---	---	87 91.98§ (no data for S.D.) Russell: personal communication	63 57.08§ (no data for S.D.) This paper	---
Lévi (1910)	Lévi (1910)	von Verschuer and Conradi (1938)			LoPresti <i>et al.</i> (1952)

§§ Average figures from Wilkins (1957).

sary; all others and Ellis (1955).

kel has reduced. From the head from the seems. The height-age t. The snub-nosed 9; for there is e these t is the tip is own in

the mean values for chronological age (taking the values for 17½ years to be the same as adult figures) but larger than that of the bird-headed dwarfs when compared with their 'height-age' standard (see Table 5).

**III. Low Birth Weight Dwarfism Attributed to Disturbance in Early Pregnancy** (Russell-Silver type; Case 7; for summary of case history see Appendix, also Fig. 10). The characteristic findings in this condition are a difference in size between the two sides of the body, together with other minor congenital abnormalities such as syndactyly and hypospadias. The facial appearance is characteristic with an underdevelopment of the lower jaw, so that the head looks relatively large. This appearance is, however, misleading as the head appears to be roughly the size to be expected from the height-age. The skeletal age is retarded and the intelligence is normal. In spite of intensive investigations, no evidence of any endocrine basis to this disorder has been discovered, though the finding by Silver *et al.* (1953) and Silver (1959) of an increased level of gonadotrophins in some of their cases suggested a gonadal deficiency. From the data at present available, it is not possible to say whether puberty is reached at a normal age. The history of an early placental disturbance which is particularly striking in Russell's series, combined with such fundamental abnormalities as an asymmetry of the body, suggests also an early disorder of development which might well be associated with a distortion of the subsequent growth pattern.

**IV. Low Birth Weight Dwarfism Attributed to Disturbance in Late Pregnancy** (dwarfed-twin type; Cases 3 and 8; for summary of history of Case 8

see Appendix; see also Fig. 5). In 1952 LoPresti *et al.* described a 21-month-old girl with a birth weight of 1.31 kg. who was one of twins, the other being normal (birth weight 2.42 kg.). In the dwarfed twin the head appeared relatively large and the intelligence was extremely low. On the basis of the very delayed skeletal development and increased sensitivity to insulin it was concluded that hypopituitarism, with some cerebral damage, was the most likely diagnosis even though the dwarfism

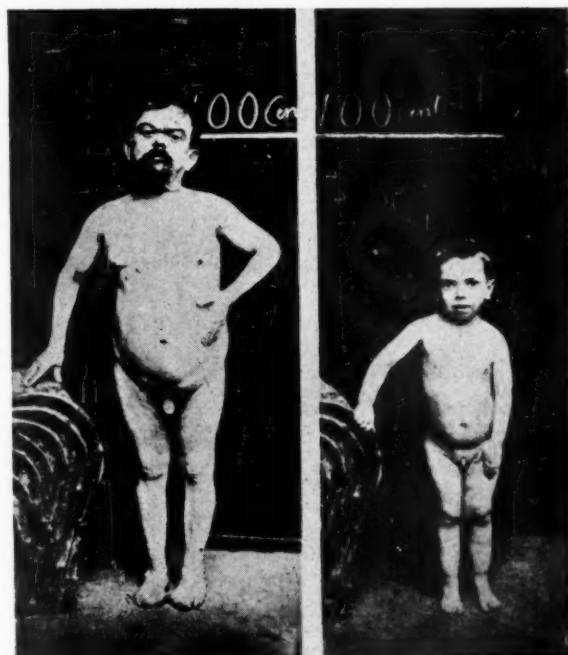


FIG. 7.—Snub-nosed dwarfism; dominant type: Cases 4 and 5 from Lévi (1910).



FIG. 8.—Snub-nosed dwarfism; recessive type: Case 6 from Verschuer and Conradi (1938).

had been present since birth. Case 3 described here shows very similar features. It can be seen from Table 5 that comparison with their height-age standards shows that in both cases the head circumference was greater than the mean value by more than  $+2$  S.D. The relatively large head is of particular interest as the same finding was described by Kirchhoff and Schaefer (1954) as being characteristic of the type of hypopituitary dwarfs of normal birth weight and without a space-occupying lesion.

It is well known that in dizygotic twins one placenta may be inadequate and that this results in a marked difference in size between the twins, but even undernutrition of this type would not produce pituitary deficiency. It is unfortunate that in neither Case 3 nor Case 8 was it possible to evaluate pituitary function more precisely.

**Possible Mechanisms.** From the preceding descriptions it appears that low birth weight dwarfism can be divided into genetically and environmentally determined types. Such a classification gives no



FIG. 9.—Snub-nosed dwarfism; recessive type: The family described by Verschuer and Conradi, showing Case 6 as 'VII 2'.

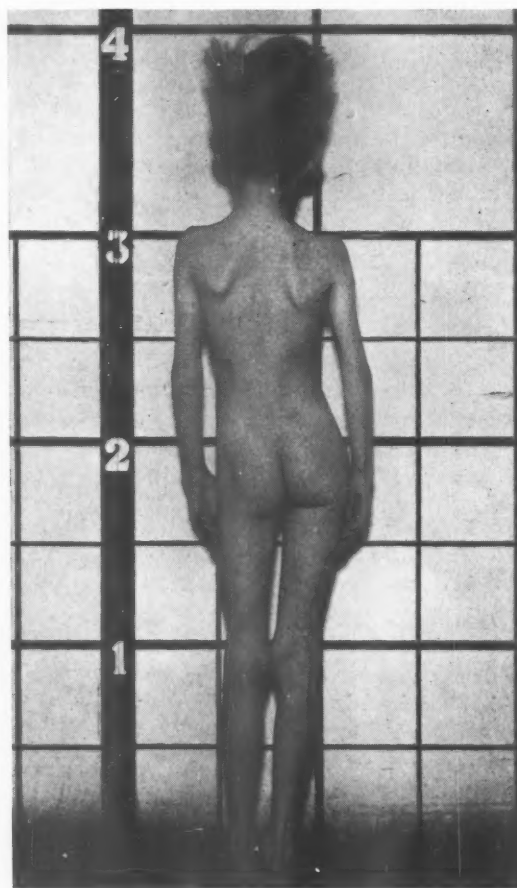


FIG. 10.—Russell-Silver type; probable placental disturbance in early pregnancy: Dr. A. Russell's case, showing asymmetry of trunk and relative shortness of left arm and leg (Case 8).

due to the immediate cause of the partial failure of growth. Even in genetically determined dwarfism the pituitary may be defective, as shown in the hereditarily dwarfed mice (Smith and MacDowell, 1950) and in the familial form of human pituitary dwarfism described by Hanhart (1953).

For dwarfism to be present before birth and to persist throughout life two possible mechanisms may be considered. Either some factor necessary for normal growth is lacking throughout the whole period, or some episode has occurred at an early stage in development, which has distorted permanently the pattern of growth to be taken by the cells of the body.

A deficiency of the pituitary is an obvious possibility, either panhypopituitarism or a deficiency of growth hormone alone. There is, however, considerable evidence that growth during foetal life and the immediate post-natal period is not affected by the absence of the pituitary. Thus, Kirchhoff and Schaefer (1954) state that in hypopituitary dwarfs without space-occupying lesions the slowing down in growth rarely occurs until well into the first year of life, and in hereditary dwarf mice growth proceeds normally until weaning (Smith and MacDowell, 1930). In rats which are born in a less mature state than humans, Walker, Simpson, Asling and Evans (1950) showed that hypophysectomy during the first 30 days of post-natal life had little effect on growth, but that a slowing down of growth occurred after 30 days. It has also been suggested that in the human foetus the pituitary is unnecessary for intra-uterine growth because infants born with complete absence of the pituitary are of normal weight (Reid, 1960). In the face of such evidence the findings in Case 3 and in LoPresti's case (Case 8, Table 5) are extremely difficult to interpret.

That factors other than the pituitary can permanently affect the pattern of growth has been shown by Widdowson and McCance (1960) who found that different levels of nutrition in the normal newborn piglet could modify the final size of the adult pig. It is therefore necessary to consider what non-endocrine factors might cause a permanently distorted growth pattern. Silver *et al.* (1953), Silver (1959) and Russell (1954) suggested that some disturbance in placental function had occurred in their cases at a very early stage in pregnancy. Seckel showed that in his Case 1 the erythrocytes, leucocytes and the epidermal cells were all normal in size, and he therefore suggested a slowing down in the rate of division of cells, from a very early stage, resulting in a reduction in the total cell mass.

### Conclusion

In this paper an attempt has been made to show that low birth weight dwarfism consists of a number of separate clinical entities. It is hoped that the suggested classification may help in the further investigation of the problem.

I would like to thank Professor Stanley Graham for his advice and for his help in the investigation of the three cases, Dr. Alex Russell for kindly allowing me to publish the description of his case, and Dr. J. M. Tanner for his help in the preparation of the paper. I also acknowledge the kind permission given by Professor Doktor Freiherr von Verschuer, Springer-Verlag, Heidelberg, and Masson et Compagnie, to reproduce the photographs which appear as Figs. 6, 7, 8 and 9.

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## APPENDIX

Summaries of case histories of reference cases taken from the literature.

**Case 4** (Lévi, 1910; Case 1, Figs. 6 and 7). Born at term. 'It appeared that right from birth, his parents had been struck by his extremely small size.' Development throughout infancy and childhood was normal and he appeared to be of normal intelligence. Axillary and pubic hair appeared at 14 years and puberty proceeded normally. His right testis was rather high in the scrotum, though easily palpable, and both testes were normal in size. The terminal phalanges of his fingers were drum-stick shaped. Radiographic examination of his skeleton showed no abnormality.

He married at 20 years a woman of average height. There were two children, both very small at birth. The first (Lévi, 1910; Case 2) is described below (Case 5) and the second died at the age of 10 years.

**Case 5** (Lévi, 1910; Case 2, Figs. 6 and 7). The first child of Case 4. He was extremely small at birth. He developed normally during infancy and childhood, but when examined at 12½ years he showed no evidence of puberty and neither testis was palpable. He appeared to be of above average intelligence. Radiographic examination showed a normal skeletal development (Lévi, 1910; p. 679) and no abnormality. In this family there were no known affected relatives in the parents' ancestry.

**Case 6** (von Verschuer and Conradi, 1938; Case VII, 2). The authors state that 'she seemed from birth onwards to be unusually small'. She was thought to be of low mentality, but had had practically no schooling. Her periods started at 18 years. She had a termination of pregnancy and a few years later another pregnancy was terminated and she was sterilized. Radiography showed no abnormality of her skeleton. The family tree showed six dwarfs occurring in three generations; there were three males and three females. In each of the three affected sibships the parents were normal.

**Case 7** (Fig. 10). (History and clinical details kindly supplied by Dr. A. Russell.) A male child, born weigh-

ing 3 lb. (1.36 kg.) and after a full-term pregnancy; during the sixth week of pregnancy the mother had 'influenza' and a brownish discharge. Apart from his small size at birth the only abnormality noted was a penile hypospadias.

At the age of 5 years 7 months he was seen by Dr. Russell on account of growth failure. He weighed 22 lb. (10.0 kg.) (<3rd percentile), his height was 37 in. (93 cm.) (<3rd percentile) and his head circumference was 19½ in. (50 cm.). It was noted at this time that the arm and leg on the left side were shorter than on the right side. He was investigated for evidence of endocrine dysfunction, but the only abnormality found was an abnormal glucose curve with a low fasting blood sugar (15 mg. per 100 ml.) and low figures at three hours (48 mg./100 ml.) and five hours (39 mg./100 ml.). When repeated at the age of 9 years 5 months the glucose curve was normal. Blood chemistry (apart from a slightly raised serum calcium of 11.6 mg./100 ml. on one occasion, later normal) was normal and tests of adrenal and thyroid function were normal. At the age of 9 years 6 months no gonadotrophins were detected in the urine. Skeletal age as assessed by radiography of the carpus was consistently less than the chronological age (at 8 years, skeletal age was 5 years).

From the age of 7 years he was treated with intermittent courses of androstalone, with little apparent result until the age of 9½ years when an acceleration of growth and weight gain occurred. There was no history of dwarfism in the family, a younger sister was normal in height and the height of the mother was 5 ft. 4 in. (160 cm.) and of the father 5 ft. 8 in. (170 cm.).

**Case 8** (LoPresti *et al.*, 1952). The second born of twins after a normal delivery. There was a slow gain in weight with several febrile episodes. Mental and physical development was very slow. Investigations showed normal serum electrolytes and blood urea. Radiography showed extreme delay in the appearance of ossification centres. The ventricular system was shown to be normal by pneumoencephalography, but there was the appearance of excessive air over the right hemisphere. There was an increased sensitivity to insulin.

# RISK OF DUAL OCCURRENCE OF MONGOLISM IN SIBSHIPS

BY

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A survey of sibships containing a mongol was undertaken to determine the risk to the mother of bearing a second mongol.

Opposing views have been expressed on the subject of familial incidence of mongolism. Benda (1947), Engler (1949) and Øster (1953a, 1956) have all stated or implied that the risk of bearing a second mongol child is no greater than the general risk of having a mongol. On the other hand, Penrose (1933) regarded the incidence of more than one mongol in a fraternity as greater than the random expectation. Böök and Reed (1950) stated that a woman who had borne a mongol had a 20 to 60 times greater chance of having another child similarly affected than if no mongol had been born in her family. Oliver (1950) concluded that the risk of a mother of a mongol having a second one was about 40 times that of any mother producing a child with mongolism. Carter, Hamerton, Polani, Gunalp and Weller (1960) referred to the experience at The Hospital for Sick Children, London, which has shown that 'the risk of parents having a second mongol child is almost certainly raised above the random risk, especially at the younger maternal ages'.

Despite these diverging views, there is a striking absence of reported extensive studies. This may be because such studies should be on a scale large enough to provide a substantial number of children born subsequent to a mongol. In the first place, because of the well-established tendency for mongols to be born to relatively old mothers, the likelihood of further children is reduced. Second, the fact of having had a mongol child may act as a deterrent to further child-bearing. Though no larger series on the incidence of mongolism among siblings born after a mongol appears to be available (the only comparably-sized series we were able to find was that of Øster (1956), which contained 343 siblings born after a mongol, among whom there were four further instances of mongolism), we realize that our numbers are not great. We record our findings,

however, with the hope that similar data will be collected from other sources, and that sufficient will become available to substantiate or modify our tentative conclusions.

## Material and Methods

The records of sibships containing a mongol were studied in two mental deficiency institutions (the Fountain Hospital, London and St. Lawrence's Hospital, Surrey), and the four district offices of the London County Council which together contain information about mongols in the whole London area. The records were compiled in the first instance by social workers who routinely visited the homes and completed a social report and history, paying particular attention to the presence of other retarded children.

The records examined at the Fountain Hospital were those of all mongols admitted from 1947 to 1959 inclusive; at St. Lawrence's Hospital, those of all mongols in the hospital at the time of the study (May 1959) and at the four London County Council district offices, those of all mongols known to the London County Council to be living at home in London at the time (April 1959). Occasionally, records of a particular sibship were present in more than one of these sources; such a sibship was counted once only. The cases studied are thus a random series of both institutionalized mongols and mongols living at home.

In each instance, a note was made of the maternal age at the birth of the mongol child who was the propositus, and at that of all known subsequent live births. The occurrence of further children with mongolism among the subsequent live births was noted. Where a mongol was a member of a twin pair, the other member of the pair was not counted as a subsequent birth. In all cases, the diagnosis of mongolism was made by medical officers familiar with the condition.

In the case of the four London County Council district offices, the child-bearing histories of the

mothers of the mongol propositi were almost always up to date at the time of the study. However, this was not so in the case of the mothers of the St. Lawrence's Hospital series and 140 of the mothers of the Fountain Hospital series. An attempt was therefore made to bring the child-bearing histories of the mothers of the propositi in these two hospitals up to date. This was done by sending out a questionnaire (Appendix A), accompanied by a brief explanatory letter, to all 96 mothers of the St. Lawrence's Hospital series and the 140 mothers of the Fountain Hospital series. Replies were received from 68 (71%) of the former and 91 (65%) of the latter. In this way an additional 29 younger siblings of the mongol propositi were traced, none of whom was a mongol.

### Results and Discussion

Records of the child-bearing histories, beginning with the birth of the mongol propositus, were obtained from the above sources in a total of 778 mothers. Information on the child-bearing histories of the mothers was up to date at the time of the study in 80% of the Fountain Hospital series, 71% of the St. Lawrence's Hospital series and practically 100% of the London County Council series, and thus in 90% of the 778 mothers. The results are shown in Table 1.

Bearing in mind that data about subsequent births were not known in some 10% of the mothers, the Table indicates that about two-thirds of the mothers of mongols do not have further children.

The incidence of mongolism was found by Carter and MacCarthy (1951) to be one in 666 maternities in London and the Home Counties, a figure close to that of other surveys of populations of European origin which have indicated an incidence of mongolism at birth of the order of one in 700 (Penrose, 1954). In our data (Table 1), there were seven second occurrences of mongolism among 367 children born after a mongol (one in 52), an incidence

some 13 times greater than that in the general population at birth. However, as the mothers of mongols are, of course, older at the birth of subsequent children, and as the incidence of mongolism rises with maternal age, significant comparisons must take account of the effects of maternal age. This is done in Table 2, using Carter and MacCarthy's (1951) findings of the incidence of mongolism at different maternal ages for comparative purposes.

Thus, taking account of maternal ages, our data indicate that the incidence of mongolism among younger siblings of mongols is 3.7 times greater (seven) than the expected incidence (1.90) if there had been no increased risk of having a second mongol. The significance of these findings can be best tested by means of the Poisson distribution which tests the probability of occurrence of rare events. Using this distribution, the probability of seven or more further mongol children occurring in the present series of younger siblings of mongols, among whom the expected incidence is 1.9, is 0.003. It would be very useful, in guiding mothers of mongols on the question of further child-bearing, if the general figure for the increased risk of bearing a second mongol could be subdivided into figures of the risk at various maternal ages. Our data are, unfortunately, too small for this purpose. However, on dividing the mothers into the two maternal age groups of under 40 years and 40 years and over, the data suggest a greater increased risk in the younger group (Table 3). This is in keeping with the experience at The Hospital for Sick Children referred to above (Carter *et al.*, 1960). Penrose (1951) noted a tendency to a lower maternal age in familial cases of mongolism. An explanation for this may be that some of these cases are due to a transmissible chromosome abnormality (Polani, Briggs, Ford, Clarke and Berg, 1960; Carter *et al.*, 1960). At least part of the additional risk of bearing a further child with mongolism in mothers

TABLE 1  
CHILD-BEARING HISTORIES OF 778 MOTHERS COMMENCING WITH THE BIRTH OF A MONGOL

Source	No. of Mothers	Sex of Mongol Propositus		No. of Mothers With Known Subsequent Live-births	% Mothers With Known Subsequent Live-births	No. of Subsequent Live-births			No. of Mongols Among Subsequent Live-births	
		Female	Male			Total	Female	Male	Female	Male
Fountain Hospital ..	244	106	138	85	35	141	58	83	1	2
St. Lawrence's Hospital ..	96	48	48	28	29	41	24	17	1	—
L.C.C. District A ..	113	60	53	30	27	50	25	25	—	1
L.C.C. District B ..	91	40	51	27	30	46	18	28	—	—
L.C.C. District C ..	114	67	47	35	31	47	22	25	1	1
L.C.C. District D ..	120	65	55	30	25	42	19	23	—	—
Totals .. ..	778	386	392	235	30	367	166	201	3	4

TABLE 2

INCIDENCE OF MONGOLISM, IN CHILDREN OF MOTHERS WHO HAVE PREVIOUSLY HAD A MONGOL CHILD, IN RELATION TO MATERNAL AGE

Maternal Age at Birth of Subsequent Child (years)	No. of Subsequent Live-born Children	Incidence of Mongolism per 1,000 Births (Carter and MacCarthy, 1951)	Expected Incidence in Subsequent Births if Risk is Not Increased	Actual Incidence in Subsequent Children
-19	0	0.00	0.00	0
20-	26	0.28	0.01	1
25-	59	0.29	0.02	0
30-	99	1.72	0.17	0
35-	102	3.52	0.36	3
40-	65	14.18	0.92	3
45-	16	26.32	0.42	0
	367		1.90	7

TABLE 3

INCREASED RISK OF HAVING A SECOND CHILD WITH MONGOLISM

Maternal Age at Birth of Subsequent Child (years)	No. of Live Births After Birth of Mongol	Expected Incidence of Mongolism in Subsequent Births if Risk is Not Increased	Actual Incidence of Mongolism in Subsequent Births	Risk Increased By
-40	286	0.56	4	7.1 x
40-	81	1.34	3	2.2 x
Totals .. .. .	367	1.90	7	3.7 x

who have previously had one affected child may be due to such transmissible defects as distinct from the usual anomaly of an additional separate somatic chromosome.

**Mongolism and Twinning.** Table 4 shows the association of twinning with mongolism among 778 mongol births. The birth was one of twins in nine instances, an incidence of twinning of one in 86 births.

By comparison, the number of twin maternities registered in England and Wales in 1955 was 8,437 in a total of all maternities of 675,026 or one in 80 (Registrar-General, 1957). The proportion of twins actually born alive was slightly less (one in 41.7), this difference from the one in 40.5 expected representing the excess of twin stillbirths over single pregnancy stillbirths. Thus the incidence of twinning in mothers bearing a mongol appears to be practically identical to that among mothers in general. On the basis of Carter and MacCarthy's (1951) finding of one mongol per 666 maternities, mongolism would therefore be associated with twinning once in approximately 57,000 births in this country.

Most of the reported cases of twinning in association with mongolism have been of twin pairs discordant for mongolism. Øster (1953b) found 9 recorded instances of mongolism in one (79) or

both (18) twins. Concordance for mongolism in twins is relatively rarer than this proportion suggests (79:18), as such pairs are more likely to be reported than discordant ones. The proportion of discordant to concordant pairs in our series was eight to one. Unfortunately, it was not possible to establish ovularity in our sets of twins. However, as Øster (1953b) found in his analysis of published reports,

TABLE 4

ASSOCIATION OF TWINNING WITH MONGOLISM AMONG 778 MONGOL BIRTHS

Maternal Age at Birth of First Mongol (years)	No. of Cases	No. Associated With Twinning	Other Twin	
			C or D*	Sex†
-19	12	0	—	—
20-	81	0	—	—
25-	101	0	—	—
30-	109	3	D	SS (M)
35-	222	2	D	SS (F)
40-	206	4	D	OS (F)
45-	47	0	D	SS (F)
			D	SS (F)
			D	OS (F)
			D	OS (F)
Totals	778	9	1 C; 8 D	6 SS; 3 OS

\* C = concordant for mongolism; D = discordant for mongolism  
† SS = same sex; OS = opposite sex.

concordance occurred only in a same-sex pair, whereas discordance was noted in both same- and opposite-sex pairs.

### Summary

The risk of another mongol being born to a mother who had already had such a child was investigated. Records from London and Surrey of 778 sibships containing a mongol were studied, the propositi consisting both of subjects living at home and those in institutions. Two hundred and thirty-five mothers of 778 mongols (30%) had known subsequent live-births, a total of 367 in all, among whom were seven second cases of mongolism (one in 52). Analysis of the 367 subsequent births, in relation to maternal age, showed a 3.7 times greater incidence of mongolism than the incidence expected if there had been no increased risk of having a second mongol. This increased incidence is statistically significant.

It is tentatively concluded that the general risk of having another mongol is increased nearly four-fold once a mother has had such a child. If similar data were collected from other sources, this conclusion could be substantiated or modified, and sufficient information would become available to subdivide the general figure for the increased risk of bearing a second mongol into risk figures at various maternal ages.

Nine of the 778 mongols were products of twin birth (one in 86) suggesting, on the basis of an incidence of mongolism of one in 666 maternities, an association of twinning with mongolism, in this country, once in about 57,000 births. Of the nine twin pairs, one was concordant for mongolism (a same-sex pair) and the other eight discordant (both same- and opposite-sex pairs).

We are grateful to Dr. C. W. J. Ingham for permission to examine the records of mongols living at home in London, and to Dr. Doreen Firmin for similar permission with regard to mongols in St. Lawrence's Hospital; to Miss N. E. S. Brian, Miss A. M. Joseph, Mrs. G. Paterson and Miss G. Russell for putting the records in their respective London County Council District Offices at our disposal, and to Dr. B. W. Richards for assistance with the St. Lawrence's Hospital records; to Miss M. F. Craib for help with collection of the data; to Dr. W. W. Holland for guidance with statistical problems; and to Dr. C. O. Carter, as well as our colleagues at the Fountain Hospital, for helpful comments.

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### APPENDIX

Questionnaire sent to mothers of mongol propositi whose available child-bearing histories were not up to date.

No. ....

1. Mother's date of birth .....
2. Name, date of birth and sex of child with mongolism  
 .....  
 .....
3. Were any children born after the child with mongolism?  
 (State Yes or No) .....
4. If yes, please state names, dates of birth and sex of all these children:  
 .....  
 .....  
 .....  
 .....  
 .....
5. Are all the children born after the child with mongolism healthy and normal?  
 (State Yes or No) .....
6. If no, please state what each one suffers from, particularly mentioning if any of them is also a case of mongolism:  
 .....  
 .....  
 .....  
 .....  
 .....

# IDIOPATHIC THROMBOCYTOPENIC PURPURA IN CHILDHOOD

BY

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Purpura is a relatively common symptom in childhood and may be due to a variety of causes. A platelet count enables one to exclude the non-thrombocytopenic variety, but more elaborate investigations are needed to exclude other primary conditions which are often associated with thrombocytopenia, e.g. leukaemia. There remains a group of patients with idiopathic thrombocytopenic purpura and it is with this disease only that the present communication is concerned.

In some cases spontaneous and permanent recovery occurs, but in others thrombocytopenia persists indefinitely, although the degree of bleeding varies from time to time. The self-limiting variety has been termed 'acute' and the persistent form 'chronic' (Hirsch and Dameshek, 1951). It should be emphasized, however, that the mode of onset may be acute in either variety and that spontaneous recovery may occur even after an illness lasting several months. At the onset it is not possible to classify cases precisely, and if death occurs early in the disease it will automatically be classified as 'acute', although not strictly self-limiting.

The pathogenesis of neonatal purpura is probably different from that of idiopathic thrombocytopenic purpura; hence cases of neonatal purpura have not been included in this article.

Purpura was originally described by Werlhof in 1775, but it was not until more than 100 years later that the association with thrombocytopenia was recognized (Osler, 1874; Krauss, 1883; Hayem, 1891). The possible role of the spleen in causation was suggested by Frank in 1915, and in the following year Kaznelson (1916) first suggested splenectomy as a method of treatment. As early as 1921 Bedson suggested that an auto-immune mechanism might be present, and this has been reconsidered recently (Evans and Duane, 1949; Harrington, Minnich,

Hollingsworth and Moore, 1951; Harrington, Sprague, Minnich, Moore, Ahlvin and Dubach, 1953).

The purpose of the present study is to define the natural history of the disease and to decide whether clinical, haematological or serological features enable an accurate diagnosis and prognosis to be made early in the disease and whether such observations facilitate the management of individual cases.

## Material and Method

During the years 1943-1958, 114 children attending this department were diagnosed as suffering from idiopathic thrombocytopenic purpura. Eighty have been observed by us during their entire illness and a further 30 during the major part. The details of the remaining four cases have been obtained entirely from the hospital records. Although this material represents all Tyneside cases referred to hospital in whom the diagnosis of idiopathic thrombocytopenic purpura was made, it cannot be claimed that it is necessarily complete.

The following investigations were carried out: The platelet level was estimated by Lempert's technique;\* the capillary fragility by the method of Hess or the negative pressure method (G. A. Smart, 1954, personal communication); the bleeding time was measured by Duke's method and clot retraction by the method of Butz-Olsen.

Bone marrow examination was carried out in all patients in whom splenectomy was contemplated, but otherwise only in cases presenting diagnostic difficulty.

Tests for platelet antibodies were performed by two methods:

**A. Direct Platelet Agglutination.** Freshly collected serum was inactivated by absorption with barium sulphate. Serial dilutions in saline were made to 10 tubes. An equal volume of washed platelet suspension in E.D.T.A./Triton WR 1339/saline media was added to each. The mixture was incubated at 37° C. for one

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\* All haematological techniques employed are essentially as described in *Practical Haematology*, 2nd ed., by J. V. Dacie. Churchill, London, 1956.

hour and any resulting agglutination was read microscopically.

**B. Tanned Sheep Erythrocyte Agglutination.** This is a modification of the technique described by Kissmeyer-Nielsen (1953). Sheep red cells treated with a dilute solution of tannic acid were coated by exposure to a platelet homogenate. The sensitized cells were suspended in serial dilutions of test sera in tubes  $5 \times 50$  mm. held in racks at an angle of 30 degrees. After three hours at room temperature the results were read macroscopically, the agglutinated cells adhering to the posterior wall of the tube, whereas non-agglutinated cells sedimented to the bottom, leaving clear supernatant fluid.

A positive control using immune rabbit anti-platelet serum and a negative control using the observer's serum were included with each batch of tests.

Finally, as the Registrar-General's returns suggested that the national death rate was much higher than that observed in this series we obtained copies of the death certificates of children registered as dying from idiopathic thrombocytopenic purpura in England and Wales during the years 1955-56. Essential clinical and haematological details of these cases were obtained from the doctor concerned and were studied to decide the actual cause of death and especially the stage of the illness at which death occurred.

### Results

Purpura was classified as 'acute' in 83 patients and 'chronic' in 31.

**Incidence.** In Fig. 1 we have shown the yearly distribution of cases during the period under consideration, and in Figs. 2 and 3 the seasonal and age distribution of the acute and chronic varieties.

The apparent incidence has not been uniform over the years for there are three well-defined peaks, the highest being in recent years, a feature also noted by other workers (Clement and Diamond, 1953).

The seasonal frequency varied with the type of purpura; chronic cases occurred all the year round and acute cases were most common in the spring and autumn.

The age distribution was the same for both the acute and chronic variety. Both were most common in young children with a maximum incidence at 7 years; similar observations have been made by Clement and Diamond (1953).

No differences associated with sex were noticed.

**The Presenting Clinical Picture.** Of the 83 acute cases, 50% gave a history of infection in the three weeks before the onset of purpura, whereas this was so for only 17% of the chronic cases. Upper respiratory infection preceded 50% of the cases, but in some there was a history of measles, rubella,

chicken-pox or dysentery. Most of these children had received some drug before admission, but in only one, a child treated with sulphonamide, was the drug thought to be a possible cause of the purpura.

Cases of acute purpura usually started abruptly, so that a child who was well one day might present covered with bruises and petechiae the next. Petechiae were most prominent in the acute variety, appearing in crops especially on the arms and legs. On the other hand purpura had been present for more than two to three weeks before first attendance in 14% of the cases that ultimately ran an acute self-limiting course.

The onset tended to be insidious in chronic cases; 50% ultimately classified as chronic gave a history of more than one year before first attendance, while a further 25% had had bruising for more than one month. Bruising usually appeared sporadically and was the predominant feature so that lesions of varying ages were usually present.

Bleeding from mucous membranes was present in one-third of all cases whether acute or chronic, but was exceptional in the absence of skin lesions. Epistaxis occurred in 28 of the 114 cases, while haematemesis, melaena, bleeding gums and bleeding after injury each occurred in about five instances.

Splenomegaly was present, but minimal, in 20% of cases, acute or chronic.

Severe anaemia was exceptional, but when present could be accounted for by blood loss except in the case of three patients who developed an acute haemolytic anaemia in the course of the primary disease.

Moderate leucocytosis was present in one-third of our cases and in many there was an excess of monocytes and large vacuolated lymphocytes. Eosinophilia was present in only two instances.

Platelet counts were performed in 106 cases when first seen; 81% had values of less than 40,000 per c.mm., while the remainder had levels of less than 100,000 per c.mm. A stained blood film was examined whenever the platelet count was performed and the platelets were often of the giant variety.

Capillary fragility was increased in 60% of cases when they first attended hospital.

The bleeding time was usually prolonged during the active bleeding phase, especially in the chronic variety (93% compared with 78% in the acute form).

Clot retraction was measured by the method of Butz-Olsen in 14 cases and by simple inspection of the clot in many more. Without exception clot retraction was impaired if the platelet count was less than 50,000 per c.mm.

Tests for platelet antibodies were done in duplicate

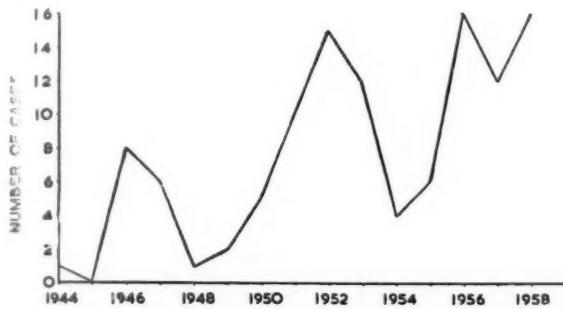


FIG. 1.—Yearly incidence of thrombocytopenia in childhood in the Newcastle area.

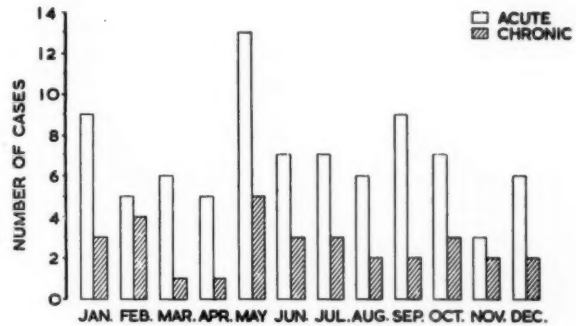


FIG. 2.—Seasonal incidence of thrombocytopenic purpura in childhood.

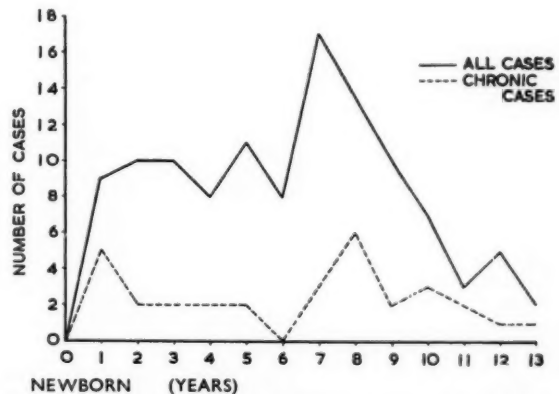


FIG. 3.—Age incidence of thrombocytopenic purpura in childhood.

by direct agglutination and the tanned red cell technique in 64 patients. Similar but not identical results were obtained with two methods and these are summarized in the Table in relation to the type of purpura and stage of the disease process.

A high proportion of positive results was obtained at all stages. Splenectomy did not appear to influence the presence of antibody, and this was borne out in six cases where tests for antibody were performed both before and after operation. Surprisingly, antibodies were frequently detected in acute cases after remission.

The form that the disease would follow could not be forecast from the results of the antibody tests.

Apart from the fact that a history of infection and an acute often florid onset suggests the acute form of purpura we have not found it possible at the onset, on clinical or haematological grounds, to predict with certainty whether the disease is likely to be acute or chronic. Haematological tests were chiefly of value in establishing thrombocytopenia and in helping to exclude other primary disease.

**Clinical Progress.** Three of the 83 cases classified as acute died within six months of the onset of symptoms. One treated by emergency splenectomy is discussed in the section dealing with splenectomy. Of the others, a girl of 4 years presented with bleeding from a tooth socket for one week, followed by one week's bruising and bleeding from gums, rectum and vagina. She was transfused on three occasions without any effect on her bleeding tendency and died six weeks after onset. No autopsy was carried out. The other, a boy aged 8 years, was admitted because of haematemesis and epistaxis on the day of admission, although he had had petechiae for the previous two weeks. Despite transfusion his condition rapidly deteriorated and he died 11 hours later. At autopsy massive gastro-intestinal bleeding was found.

The other 80 recovered, 44 within one month, 25 between one and four months, and 11 after a longer period. The longest period associated with complete spontaneous recovery was two and a half years, but in three additional children symptoms persisted for more than one year before remission occurred.

Symptomatic improvement occurred first followed by a return to normal capillary fragility, while platelet counts only reached normal values approxi-

TABLE  
PLATELET ANTIBODY IN RELATION TO  
CLINICAL TYPE OF PURPURA

Classification of Idiopathic Thrombocytopenic Purpura	No. of Cases	Strong Positive	Weak Positive	Negative
Active acute .. ..	11	5	1	5
Active chronic .. ..	14	8	3	3
Recovered acute .. ..	30	13	10	7
Chronic after splenectomy ..	9	6	1	2
Total .. ..	64	32	15	17

mately three weeks after symptomatic improvement. For the acute variety of the disease, the mean duration of symptoms was 4.4 weeks, but of thrombocytopenia 7.5 weeks.

Once the platelet count has returned to normal remission is usually permanent, although in two instances further relapse occurred. One girl presented at the age of 7 years with haematuria and severe bruising, but within seven weeks she had completely recovered and her platelet count was 300,000 per c.mm. Three months later, however, she had a further episode of haematuria associated with thrombocytopenia. Recovery occurred within five weeks and has been maintained now for two years. The other, also a girl, presented at 5 years with bruising and petechiae following an infective illness five weeks before. Spontaneous recovery occurred within three months, but further bruising associated with thrombocytopenia recurred one month later. This relapse lasted only four weeks, since when the child has been perfectly well for two years.

The remaining 78 survivors have been kept under observation for periods of three to 18 years, and half of them for more than 10 years. None have relapsed. On their last visit three had platelet counts of only 150,000 per c.mm., but the remainder were in the range of 200-500,000 per c.mm., with an overall average of 300,000 per c.mm.

The remaining 31 cases were classified as chronic purpura.

One child who developed purpura in infancy died after one and a half years from a presumed cerebral haemorrhage. In view of her age splenectomy was not performed and corticosteroids were not available at this time.

Of the remainder, 16 have been treated by splenectomy. The other 14 have been observed for periods varying from three to 12 years (average five years) during which the average platelet level has been 63,000 per c.mm. Splenectomies were not performed because of the potential risk of infection after operation and because their symptoms were minimal, e.g. W.B., a manual worker now aged 22 years, developed idiopathic thrombocytopenic purpura at the age of 10 years. During the 12 years of observation his platelet count has never been higher than 40,000 per c.mm., but apart from excessive oozing following teeth extraction he has had no disability. Some are females who have passed puberty without excessive menstrual bleeding.

#### Management

When planning the conduct of any individual case of idiopathic thrombocytopenic purpura one must

bear in mind that the risk of death is greatest in the initial acute phase, although it is present as long as thrombocytopenia persists. One in three cases persist indefinitely, but spontaneous recovery will occur within one year of onset in the other two.

Symptomatic treatment is often indicated and 25% of our patients had received antibiotics for upper respiratory infections before coming into hospital. No effect on the purpura was evident.

Blood transfusion was given only if blood loss had been sufficient to produce anaemia or shock; it was needed in the acute initial phase in 13 patients. Twelve additional children needed transfusion during the chronic stage of the disease. The urgency of transfusion usually precluded the use of platelet-rich blood, but in any case we think that this is only rarely indicated for any effect on the platelet level is trivial and short-lived. Moreover, injected platelets may lead to the development of platelet antibody. On only two occasions did we use platelet-rich blood, once because of persistent bleeding from a tooth socket and once as cover for teeth extraction. The haemostatic effect in the first boy was dramatic, although no rise in platelet count was evident. The second boy had little bleeding at operation, but this was also the case in six out of eight other children undergoing teeth extraction. The other two required transfusion because of persistent bleeding.

**Corticosteroids.** We have only tried corticosteroids in selected cases. Seven were treated during the initial acute phase, three when first seen but when purpura had already been present for one to three months, and before splenectomy in five cases of chronic purpura.

Usually we have given 200 mg. of cortisone or 40-50 mg. of prednisone daily during the first week of treatment, the dosage being decreased during each succeeding week and not continued for more than one month in most patients.

Of the seven treated early, four remitted but three showed no improvement at all and developed chronic purpura. Of the four who responded, two did so within one week, one within a month, although symptomatic improvement was immediate, while the other had active bleeding during the first week of corticosteroid therapy, although remission was complete within one month.

Of the three patients with the longer history before treatment, one remitted within one month, but there was no effect at all in the other two.

Of the five given corticosteroids before splenectomy, one showed a slight decrease in bleeding

tendency and another a transient small rise in platelets. The other three derived no benefit at all.

One other child who developed an acute haemolytic anaemia with positive Coombs test during the course of chronic idiopathic thrombocytopenic purpura was treated with prednisone. The anaemia responded promptly, but neither the bleeding tendency nor platelet level was affected.

**Splenectomy.** Sixteen patients in this series were treated by splenectomy because of persistent thrombocytopenia of more than one year's duration, together with excessive bleeding. The remaining 14 with persistent thrombocytopenia, but with little disability have been left untreated.

Bone marrow examination before operation was carried out in all. The number of megakaryocytes was increased in five cases, decreased in four and normal in the remaining seven. Without exception the proportion of megakaryocytes actively producing platelets was markedly decreased. Two patients had a significant increase in eosinophils in the marrow. We did not find the myelogram helpful in predicting the probable response to splenectomy, nor did we find that the presence of platelet antibodies gave any indication of the likely response to splenectomy.

We estimated the platelet count and bleeding time at the start of operation, when the splenic pedicle was clamped, and at the end of operation in five cases. No significant change in either test was observed. In some cases, however, an increase in the platelet count was noted within 30 minutes of operation and counts in the order of 100,000 per c.mm. were occasionally recorded within three hours. Usually, however, a significant increase was only observed at about six hours and levels greater than 100,000 per c.mm. were reached within 24 hours.

Figs. 4 and 5 show the platelet response after splenectomy in five cases of idiopathic thrombocytopenic purpura and five cases of congenital spherocytic haemolytic anaemia.

It will be seen that in idiopathic thrombocytopenic purpura peak values were usually reached between three to eight days; thereafter they fell to low normal values which were maintained. The higher the initial response the higher the ultimate equilibrium (average 350,000), although one case with a poor initial platelet rise eventually responded equally well.

In congenital spherocytosis the response was slower, but similar maximal levels were achieved and many had values of more than 100,000 per c.mm. several years after operation.

Emergency splenectomy was performed in only

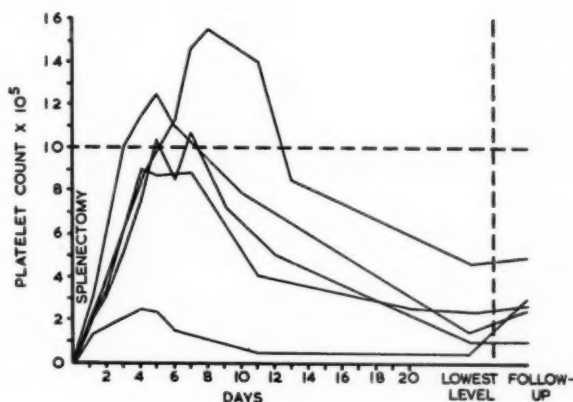


FIG. 4.—Platelet counts after splenectomy for idiopathic thrombocytopenic purpura.

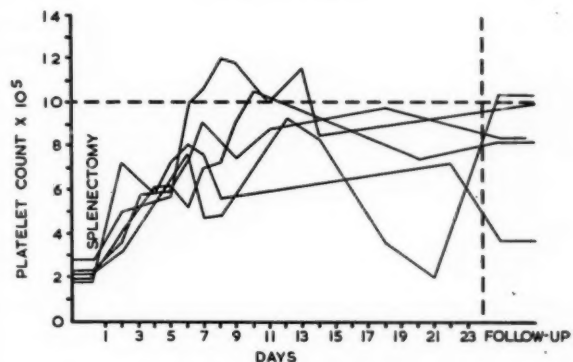


FIG. 5.—Platelet counts after splenectomy for congenital haemolytic anaemia.

one patient, a child aged 20 months. The illness presented with epistaxis, haematuria and melaena 10 days after an attack of measles. Bleeding continued for eight days at which stage splenectomy was performed. For two days there was some improvement, then epistaxis and melaena recurred, and on the seventh post-operative day jaundice developed. On the twelfth post-operative day the wound broke down and later a faecal fistula and pyopneumothorax developed. Bronchopneumonia supervened and the child died three weeks after operation. It is not possible to say to what extent splenectomy contributed to the severe infection, but it is certain that in this case it had little effect on the bleeding tendency. This case occurred before corticosteroids were available.

The 16 patients treated by splenectomy have been followed up for periods of two to eight years. Initially all responded completely, but thrombocytopenia has recurred in two. Neither has serious disability, but platelet antibodies have been detected in both.

Two boys treated by splenectomy have had serious infection since, and it seems possible that this is a consequence of operation. One developed purpura at the age of 6 months and was admitted to hospital on four occasions because of bleeding before the age of 4 years. At this time he developed a Coombs positive haemolytic anaemia and was treated with corticosteroids before splenectomy was carried out. Thrombocytopenia persisted, although his anaemia subsided, but 18 months after operation he developed pneumococcal meningitis. In the five years since operation he has had further attacks of pneumococcal and influenzal meningitis, two generalized septicaemic illnesses and repeated respiratory infections with pneumonia on at least three occasions. The other boy first developed purpura at the age of 7 years and was treated by splenectomy at the age of 10 years. Three months after operation he developed a generalized pneumococcal septicaemia and was admitted *in extremis* within hours of onset with severe peripheral circulatory failure. A tracheotomy was required and he was treated with steroids and antibiotics; he survived after a prolonged illness. So severe had been the peripheral collapse that some of his toes suffered ischaemic necrosis and had to be amputated subsequently.

#### Death due to Idiopathic Thrombocytopenic

##### Purpura in England and Wales in 1955 and 1956

Fifty-eight children under the age of 11 were registered as having died from idiopathic thrombocytopenic purpura in these two years.

Twenty-seven of these deaths were in fact due to anaphylactoid purpura. Details of 30 of the remaining 31 were obtained, but eight were excluded as there was insufficient evidence on which to make the diagnosis. Ten of the remaining 22 were newborn babies, four of these deaths being associated with severe congenital defects. There remained only 12 comparable with the present series; and eleven were due to intracranial haemorrhage and the other to massive bleeding into the gastrointestinal tract.

One death occurred after an illness of 21 months' duration, but all the others occurred within five months of the first symptom. Several died after an extremely short illness, e.g. one child died within 24 hours of the onset and five more within one week. Two children developed signs of cerebral irritation while at school and died within a few days. More than 50% of the deaths occurred within 12 days of the first symptom and the onset was sudden in all. It is of interest that eight of the 12 fatal cases were admitted because of mucous membrane haemor-

rhage, haematemesis, and melaena in five and haematuria in three, although all eight gave a history of previous bruising.

None of the deaths could be attributed to lack of treatment for as well as blood transfusion in nearly every case, eight received corticosteroids and three were treated by splenectomy. One child was treated by splenectomy in the acute phase because of signs of cerebral haemorrhage, but died shortly afterwards with extension of this; two were treated in the sub-acute phase but showed no response. One died immediately after operation due to bleeding into the bowel; the other child died from cerebral haemorrhage despite the continuous administration of corticosteroids.

#### Discussion

In this communication we are concerned only with idiopathic thrombocytopenic purpura in childhood.

The natural course of the illness varies, especially in different age groups, but even in childhood variation is common. Some recover completely within a few days; others die due to exsanguination or bleeding into vital organs, while in others symptoms may persist indefinitely. The acute self-limiting variety is common in childhood (Simpkiss and Cathie, 1954; Komrower and Watson, 1954) and comprised 75% of the present material.

Like other workers (Clement and Diamond, 1953; Simpkins and Cathie, 1954; Lozner, 1954) we found an equal sex distribution, although the latter recorded a female to male ratio of 3.7 to 1 in adult cases. In the series reported by Komrower and Watson, 23 of the 24 acute cases recovered in three months; half of these recovered in six weeks. In the present series more than half recovered within one month, 85% in four months, but spontaneous recovery was observed as long as two and a half years after onset. Carpenter, Wintrobe, Fuller, Haut and Cartwright (1959) recorded spontaneous remission up to one year after onset, but none after this time.

Although acute idiopathic thrombocytopenic purpura may carry the better ultimate prognosis, the initial stage of this disease is most dangerous, for three of the four deaths in our material occurred shortly after onset and 14 children required blood transfusion. Komrower and Watson (1954) reviewed the literature concerning 278 cases of idiopathic thrombocytopenic purpura in childhood. Nineteen died, 17 within one month of the onset of symptoms. Of the remaining two deaths, one occurred 13 months after splenectomy and the other was due to chronic nephritis. As we have seen, there were 12 deaths from idiopathic thrombocyto-

purpura in childhood in England and Wales in 1955 and 1956. Eleven died from cerebral haemorrhage and one from gastro-intestinal bleeding. The onset was sudden in all and over half died within 12 days of the first symptom in spite of active treatment, including blood transfusion, corticosteroids and splenectomy.

It seems, therefore, that while thrombocytopenia always carries a potential risk it is greatest in the early stage of the disease, especially when it is characterized by florid bruising and mucous membrane haemorrhage.

Energetic treatment is indicated in all such cases, but because of the tendency to spontaneous remission it is difficult to evaluate the true benefit of such treatment. Like Watson-Williams, MacPherson and Davidson (1958) we found that a short history, especially if the illness was preceded by infection, usually indicated acute idiopathic thrombocytopenic purpura, whereas a long history with an indeterminate time of onset indicated the chronic form. These authors thought that steroids hastened remission in the acute group, but it is probable that remission would have occurred in any case. The good results achieved by splenectomy in their cases could similarly be explained. Byrne (1950) and Elliott and Turner (1951) recommend splenectomy in the first attack of purpura, but in our opinion it should not be carried out early in the disease for the mortality in emergency splenectomy may be as high as 80% (Wintrobe, 1951; Komrower and Watson, 1954; Simpkins and Cathie, 1954).

In the past decade platelet transfusion has become a practical proposition (Hirsch and Gardner, 1952; Tullis, 1953; Klein, Toch, Farber, Freeman and Fiorentino, 1956; Gardner and Cohen, 1960; Tobin and Friedman, 1960), but its value in idiopathic thrombocytopenic purpura is limited, for although the life of circulating platelets is about one week in normal people, it is probably only a matter of hours in patients with idiopathic thrombocytopenic purpura (Harrington *et al.*, 1953; Stefanini, Chatterjea, Dameshek, Zannos and Santiago, 1952). It has been suggested that the benefit may be out of proportion to and may outlast the number of circulating platelets (*Lancet*, 1953). Platelet antibodies may develop in response to platelet transfusion and this may be a contraindication especially in idiopathic thrombocytopenic purpura (Sharp, 1956). Although there may be a place for platelet transfusion in other thrombocytopenic states such as aplastic anaemia or after irradiation (Woods, Gamble, Furth and Ligelow, 1953) it is only necessary in exceptional circumstances in idiopathic thrombocytopenic pur-

pura, since teeth extraction and splenectomy may be carried out in such patients without excessive bleeding.

If neither splenectomy nor platelet transfusion is indicated in the acute phase of purpura then we must rely on steroid therapy to control dangerous haemorrhage. Various workers (Robson and Duthie, 1950; Faloon, Greene and Lozner, 1952; Jacobson and Sohler, 1952; Wilson and Eisemann, 1952; Greene, Faloon and Lozner, 1953; Hävermark and Nordenson, 1953; Lozner, 1953) consider that steroids rarely influence the platelet level, but produce their effect by decreasing capillary permeability.

Carpenter *et al.* (1959), however, reported complete remission in 38% of cases treated by steroids. Dameshek, Rubio, Mahoney, Reeves and Burgin (1958) went further and claimed complete remissions in 10 out of 11 patients with acute and 12 out of 19 patients with chronic disease; although all were not permanent, they said that further remissions could be produced and maintained by continuous therapy. In addition, they were of the opinion that prednisone was superior to cortisone or A.C.T.H.

Response is particularly good in children and in the acute form of purpura, but it seems to us that complete remission is more likely to be a natural feature of the disease rather than a result of steroids *per se*. Harrington *et al.* (1953) gave steroids to human volunteers and thereby prevented the development of thrombocytopenia when immune serum from thrombocytopenic patients was administered.

We believe that a one month's course of corticosteroids should be given to any child presenting with purpura of acute onset, especially if florid bruising or mucous membrane haemorrhage is present. Bleeding may diminish even though the platelet count is not altered. Continuous therapy in cases of chronic idiopathic thrombocytopenic purpura with mild symptoms is not indicated.

If complete remission occurs with return of platelets to normal values, cure is likely to be permanent. If thrombocytopenia persists for more than one year, spontaneous remission is unlikely and splenectomy should be considered. The possibility of cure and risks of splenectomy must be assessed in relation to the dangers of persistent thrombocytopenia. Most fatal haemorrhages occur in the acute phase, but there are exceptions. Simpkins and Cathie described a girl who after three and a half years of relatively mild idiopathic thrombocytopenic purpura developed uncontrollable haemorrhage and died with intracranial bleeding. They also mentioned a similar case where death occurred in similar

circumstances seven years after the onset of purpura. One death in the present series occurred after prolonged illness, while the same was true of two of the fatal cases in England and Wales in 1955 and 1956.

Splenectomy is a safe operation in chronic purpura, but it may predispose to infection in some individuals. Early reports suggested that this complication was restricted to young infants (King and Shumacker, 1952), but recent observations have established that this risk is not restricted to any age group (Gofstein and Gellis, 1956; Smith, Erlandson, Schulman and Stern, 1956, 1957; Doan, Bouroncle and Wiseman, 1960; Lucas and Krivit, 1960; Robinson and Sturgeon, 1960).

Huntley (1958) reviewed 58 cases of splenectomy in infants and children of which 46 had been followed up satisfactorily. She suggested that infection was more likely in young children and especially so if the primary disease was one associated with an increased risk of infection; this is the case in Aldrich's syndrome (Aldrich, Steinberg and Campbell, 1954).

Infection may occur years after splenectomy (Robinson and Sturgeon, 1960). C. H. Smith (1958, personal communication) recommends prophylactic penicillin for at least two years after operation, and also that any infection which does occur should be treated energetically from the start. Carpenter *et al.* (1959) reported the development of disseminated lupus erythematosus in one of their cases, a risk previously reported by Dameshek *et al.* (1958), but Doan *et al.* (1960) deny that this is a risk. Three children in our series developed serious infections after splenectomy.

We consider that where symptoms are minimal splenectomy should be withheld and close supervision employed.

Not all cases of chronic idiopathic thrombocytopenic purpura treated by splenectomy are cured, and Lozner (1954) estimated that there was a 60% chance of cure, that a further 20% improved, but that 20% derived no benefit. On the other hand, Carpenter *et al.* (1959) reported satisfactory results in 81% of their cases and in the present series 14 of the 16 cases treated by splenectomy were cured and the other two were improved, although thrombocytopenia recurred. Carpenter *et al.* (1959) reported relapse in two of their cases after a good initial response lasting over two years.

Schwartz and Kaplan (1950) suggested that a raised eosinophil count in the marrow indicated an allergic background and that spontaneous remission was therefore probable. They suggested that splenectomy was indicated only if the eosinophil count was normal, but most workers have not

been able to confirm this (Presley, Best and Limarz, 1952; Simpkins and Cathie, 1954; Komrower and Watson, 1954). Indeed, Lozner (1954) suggested that a raised eosinophil count indicated a good response. We did not find that the eosinophil count in blood or marrow was of any value. It has been suggested that the number or morphology of the megakaryocytes is of value in predicting response to splenectomy (Dameshek and Miller, 1946; Valentine, 1947), but we and many others have not found this (Diggs and Hewlett, 1948; Komrower and Watson, 1954; Simpkins and Cathie, 1954).

It is disappointing that the presence of platelet antibody does not help in predicting the probable response to treatment (Dameshek and Stefanini, 1955). This was certainly borne out by our own observations, but it seems possible that such tests may be of most value in predicting the risk of neonatal thrombocytopenic purpura, even in the infants of mothers who have been treated, perhaps successfully, by splenectomy.

Lozner (1953, 1954) studied the value of giving steroids before carrying out splenectomy; no complications after operation were observed, but there was no correlation between the response to steroids and the response to splenectomy, and this is in accordance with our observations.

Thrombocytopenia in childhood is a potentially dangerous condition. If there is any underlying cause this should be treated appropriately. Otherwise corticosteroids should be administered in adequate dosage at the onset unless symptoms are minimal or of long duration. If there is no response in a short period of time it is unlikely that there will be and as continuous steroid therapy may be dangerous it should be discontinued. If thrombocytopenia persists for more than one year splenectomy should be considered, for in 80% of cases it will often produce permanent benefit. There is a potential risk of severe infection after splenectomy which may be greater in infancy and in conditions with an infective element, but the risk in idiopathic thrombocytopenic purpura does not seem to be disproportionately high.

#### Summary

One hundred and fourteen cases of idiopathic thrombocytopenic purpura in childhood were observed during the years 1943-1958. Of these, 83 were of the acute self-limiting variety and 31 of the chronic variety.

Clinical and haematological findings have been evaluated in relation to management and differentiation of the two forms of purpura.

Tests for platelet antibodies were performed in 64 patients and their significance is briefly discussed.

The circumstances preceding death were examined in this series and also in all fatal cases in England and Wales during 1955 and 1956.

The role of corticosteroids and splenectomy in management is outlined.

We are indebted to the various members of the Department of Child Health and to paediatricians in the Newcastle region for referring cases and allowing us access to the clinical records, and to the Registrar-General for copies of death certificates and to the many doctors who supplied clinical details of fatal cases. Dr. S. G. Owen and Dr. Alan Sharp gave us much valuable assistance with the serological tests for platelet antibodies. The other haematological tests were performed by the technical staff of the Child Health Laboratory, Royal Victoria Infirmary.

The majority of the cases treated by splenectomy were under the care of Professor Andrew Lowdon.

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# ECTROMELIA

## A CASE REPORT

BY

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The following case is considered worth reporting on account of the rarity of major degrees of congenital hypoplasia of the limbs.

### Case Report

The mother, age 29, was a multigravid patient having had one 12-week spontaneous abortion and a live normal baby for which caesarean section had been performed for a failed trial of labour; the infant weighed 7 lb. 10 oz. at birth. This pregnancy had been uneventful during the early months apart from a severe anxiety state; the patient had a hysterical personality, for which she required psychiatric treatment but no drugs were administered. There was no history of influenza or any other viral infection in early pregnancy and no anaesthetic was administered. The foetus presented by the breech and the malpresentation could not be corrected easily when an external cephalic version was attempted. In view of this and the history of the previous successful pregnancy, an elective caesarean section was performed at 39 weeks gestation. A living female ectromelus was delivered, which died 24 hours later.

**External appearance.** The body was that of a female measuring 33 cm. from crown to rump, weight 4 lb. 13 oz. (2,180 g.). The upper limbs were completely absent and the lower limbs represented only by abnormal feet attached directly to the pelvic girdle (Fig. 1). The right appendage was 3.7 cm. in length with the heel directed posteriorly with one rudimentary nail-bearing digit. The left appendage was 4.7 cm. long with the heel directed laterally and with three nail-bearing digits.

Radiographs revealed one metatarsal in each appendage with one set of phalanges in the right and two in the left (Fig. 2). No bones were present beyond the upper limb girdle. There were no other skeletal deformities.

The placenta, membranes and umbilical cord appeared normal with two umbilical arteries present.

### Internal Examination (Dr. J. M. Preece).

**Heart and Great Vessels.** Both atria appeared normal, as also did the atrial septum. The aorta was enlarged and arose from the right ventricle where its opening lay astride a high ventricular septal defect. The aortic

valves and openings of the coronary arteries appeared normal. A minute pulmonary artery, with a considerable degree of stenosis at its origin, arose from the left ventricle and was connected to the aorta beyond the stenosis by a patent ductus arteriosus. The origin of the vessels from the thoracic aorta appeared normal, but the first two bronchial arteries were much larger than usual.

**Kidneys.** The right kidney was represented by a



FIG. 1.

lobulated cystic mass with no macroscopic evidence of remaining renal tissue. The left kidney appeared normal.

All the other organs appeared normal.

**Organ Weights.** Brain: 343 g.; spleen: 6 g.; left lung: 46 g.; left kidney: 7 g.; right lung: 46 g.; right kidney: 37 g.; liver: 73 g.; thymus: 3 g.; suprarenals: 2 g.

**Histology.** The lung section showed congestion; the liver section showed small foci of haemopoiesis. Section of the right kidney showed it to consist of mesenchymal tissue with small numbers of grossly dilated ducts lined by cuboidal epithelium. No glomeruli were present. Section of the left kidney showed no abnormality. The pancreas, suprarenals and thymus were normal.

### Classification

No satisfactory classification of developmental failure of the limbs exists. The definitions followed by most authors are those given in *Blakiston's New Gould Medical Dictionary* (1949) and are as follows:

**Peromelia** (G. *pēros*, maimed; *melos*, limb): Congenitally deficient, stunted or misshapen limbs.

**Amelia** (G. *ā*, not): Congenital absence of all extremities.

**Ectromelia** (G. *ectrōsis*, miscarriage): One or more congenitally imperfect limbs.

**Hemimelia** (G. *hēmi*, half): Incomplete or stunted extremities.

**Phocomelia** (G. *phōkē*, seal): Absence or markedly imperfect development of arms and forearms, thighs and legs, but with hands and feet present.

The term peromelia may be used generically and needs no further comment. Poidevin (1953) is of the opinion that, for true amelia, there should be no limb bones whatsoever beyond the limb girdles. On this basis he found only eight cases of amelia in the literature. A further case has since been described by Illemann-Larsen (1954). If phocomelia is defined by a similar strict definition, there should be no limb bones present between the limb girdles and the hands and feet, but this is impractical as no case of this nature has been described. The term is well worth retaining and should be extended to include any cases where hands or feet or both are attached almost directly to the trunk, giving the flipper-like appearance from which the name is derived. A fascinating historical review of these unfortunate individuals, including the famous 'Pepin', is given by Gould and Pyle (1898) who also describe examples of the other types of peromelia. A more recent case is that of 'Minnie', a 30-year-old negress with normal lower limbs (Hill, 1937).

The above definition of hemimelus is unsatisfactory and does not signify the essential nature of the lesion which is a deficiency of the distal parts of the limbs, which taper to a stump, while the proximal segments are normal. The term is little used. All remaining cases are classified as ectromelia, but the exact degree to which a limb must be stunted to come within the definition is not easy to assess. Some authors include such minor defects as the absence of digits. It is recommended that only major degrees of malformation should be included, but it seems impossible to define this further. It certainly cannot be assessed by interference with function.

### Aetiology

Developmental failure of the extremities may be genetically determined or arise during foetal development. The role of Simonart's threads (amniotic bands) associated with the condition of *graviditas examnialis* is no longer considered an important factor in the production of these deformities. There are only two reports in the literature of peromelia in siblings. O'Brien and Mustard (1921) describe an ectromelus, which they call a phocomelus, occurring in a family in which three members were affected, whilst Flachsland (Gould

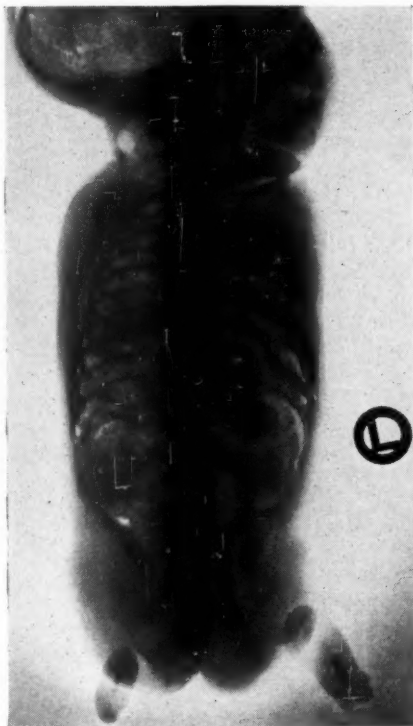


FIG. 2.

and Pyle, 1898) reports on a woman who had three times borne children without arms and legs.

According to Arey (1954), all the materials for the limb are present within the limb bud when it first appears late in the fourth week. The limb primordium, even when barely discernible as a slight swelling, is capable of self-differentiation when it is isolated and without nerve supply. The normal source of induction is not obvious. By the application of metabolic procedures at the time of the development of the limbs, ectromelia has been produced in mammals (Kalter and Warkany, 1959). A wide range of teratogenic agents and methods have produced these deformities. These include deficiencies of vitamin A, riboflavine and folic acid; hypervitaminosis A; the administration of nitrogen mustards, nucleic acid antagonists, insulin, tryptan blue and carbon monoxide. This last factor, which probably exerts its effect through the production of anoxia, may be of importance in cases of attempted suicide. Bette (1957) reports a case of ectromelia in association with this condition, and the author has recently had a similar case, whilst Ingalls (1960) records a further case as well as two other cases associated with anoxia in early pregnancy. The increasing habit of self-

administration of cytotoxic drugs in order to induce abortion will probably produce further cases.

### Summary

A case of ectromelia associated with other congenital deformities is described.

The classification and aetiology of developmental failure of the limbs is briefly discussed.

I wish to thank Sir John Peel, under whose care the mother was admitted, and also Dr. B. S. Cardell for the post-mortem report.

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# PULMONARY OEDEMA IN ACUTE GLOMERULONEPHRITIS

BY

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Pulmonary oedema in association with acute glomerulonephritis is uncommon (Wood, 1956; Nelson, 1959), and the pathogenesis is as yet far from clear. De Wardener (1958) states that 80% of the cases of acute nephritis recover completely and 5% die in one or two weeks of either acute cardiac failure, acute renal failure or hypertensive encephalopathy. The remaining 15% subsequently develop chronic nephritis. Cases dying in acute cardiac failure, therefore, are rare. Whether the pulmonary oedema in these cases is due to acute cardiac failure or not will be discussed later.

This paper gives an account of three children who suddenly developed the clinical features of acute pulmonary oedema. A discussion of the pathogenesis with special reference to renal diseases is given.

## Case Reports

**Case 1.** A girl aged 11½ years, the eldest child of an Italian family with three other children, was admitted on October 10, 1959.

**Family History.** The three younger children were well, apart from recent colds. They had attended their doctor frequently for upper respiratory tract infections and otitis media. Two other children had died in Italy before immigration, one, when 9 days old, from congenital abnormalities and the other from meningitis when 2 months old. The father had been in bed with 'influenza' during the past week, otherwise he had always been well. There were no other family illnesses.

**Previous Illnesses.** She had always been a healthy robust girl and had never really been ill before. She had had measles and mumps, but had not had any immunizing injections.

**Present Illness.** For one week before admission to hospital she had had a cold and a discharging ear. Three days before admission she still had a discharging ear, temperature 102° F., and her doctor was called. He diagnosed acute tonsillitis and gave a penicillin injection, 900,000 units. The next day she was a little

better. The temperature had fallen to 99° F. and she was given another injection of penicillin. On the morning of the following day she complained of abdominal pain centred mainly over the right iliac fossa. The temperature was 98° F. and pulse rate 90 per minute. The child became somewhat hysterical at the thought of another injection, so this was not given.

Because of the abdominal pain, her doctor called again at 8 p.m. when the abdomen was normal, but he noticed a very slight grunt in her breathing. The rate was slow and she was sleeping comfortably. The mother stated she had a fleeting rash since the last injection. During the evening she became progressively more short of breath, developed a cough and had to sit up in bed. The window was opened to help her to get more air. By 4 o'clock the next morning she became so distressed she was brought to the hospital.

On admission her temperature was 99° F., pulse 128 per minute; she was very dyspnoeic, was sitting up, and was restless and cyanotic. She was a rather plump Italian girl with no peripheral or facial oedema. She had a discharging right ear and the fauces were red. Trachea was midline. Heart rate was rapid with normal findings on auscultation. In the lungs there were scattered râles mainly at the bases and a reduced air entry at the left base. Blood pressure was 140/90 mm. Hg. No other significant abnormality was found. The urine was not tested owing to the difficulty of collecting a specimen. A provisional diagnosis of a left-sided pneumonia was made and she was treated accordingly with oxygen, intramuscular chloramphenicol 500 mg. *statim* then 200 mg. six-hourly, intravenous aminophyllin 240 mg. and paraldehyde 2 ml. intramuscularly to help control her restlessness. A throat swab showed *Streptococcus viridans* only. Chest radiographs of both lung fields showed widespread interstitial pulmonary oedema and the cardiothoracic ratio was increased (Fig. 1).

From admission at 4 a.m. on October 19, 1959, to death at 2.35 p.m. the next afternoon her course was progressively downhill. She improved temporarily with oxygen, but later became more dyspnoeic, restless and cyanosed. At 12 noon her condition worsened and much blood-stained frothy mucus was coughed up from her mouth. Intravenous injections of digoxin 0.5 mg. and hydrocortisone 50 mg. were given at this stage.

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FIG. 1.—Chest radiograph: both lung fields show widespread interstitial pulmonary oedema; the cardiothoracic ratio is probably increased.

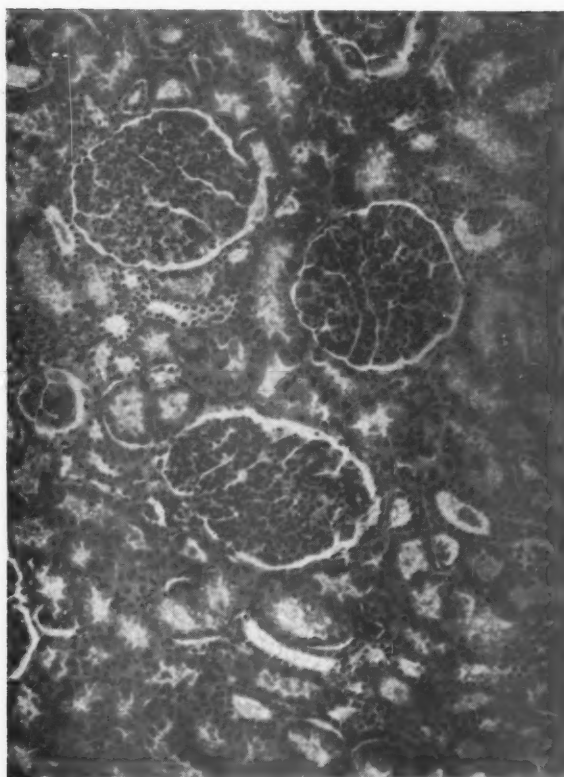


FIG. 2.—The glomerular tufts of the kidney are enlarged, hypercellular and vascular. (H. and E.  $\times 85$ .)

The salmon pink frothy mucus increased in amount and obstructed her airway, and in spite of attempts to clear this she died at 2.35 p.m.

*Autopsy.* (PM 121/59 A.C.H.)

**PLEURAL CAVITIES.** Each contained approximately 350 ml. of clear yellow fluid. Trachea contained a moderate amount of watery fluid streaked with fibrinous threads. Lungs were dull purple and heavy, and on incision airless and oedematous. Pericardium contained approximately 75 ml. of clear straw-coloured fluid. Heart weight was 170 g. (normal is 124 g.). The left ventricle was moderately hypertrophied and the right ventricle dilated. Kidneys: the weight of the right was 99 g.; left, 94 g. On incision the cortex was increased in depth and pale with fine red streaks and very small white glistening glomeruli projecting from the cut surface. The medulla was deeply congested. A blood urea nitrogen performed on post-mortem blood was 22 mg./100 ml.

**MICROSCOPIC EXAMINATION.** In the kidney glomeruli (Fig. 2) the tufts were comparatively avascular and hypercellular and infiltrated with small numbers of polymorphonuclear leucocytes. Some showed an exudate of red blood cells in the capsular space. A few tubules contained red blood cells while others contained an eosinophilic amorphous material. The capsular epithelium showed no crescent formation, nor was there fibrosis of any glomeruli. The interlobular arterioles and afferent arterioles were normal and there was no infiltrate in the interstitial tissues. Lung alveoli were expanded and the walls slightly thickened and congested. Many alveoli contained a finely granular and sometimes fibrillar exudate which in places showed a tendency to condense against the alveolar wall, forming a membrane. In addition there was a cellular exudate composed principally of red blood cells with a few polymorphonuclear leucocytes and macrophages. No eosinophils were seen.

In summary the autopsy revealed bilateral pleural effusion; pulmonary oedema; cardiac hypertrophy, and kidneys with prominent hypercellular avascular glomeruli. The immediate cause of death was pulmonary oedema; the primary cause, acute nephritis.

*Comment.* Unfortunately no urine was available at autopsy for examination. However, the diagnosis of acute nephritis is certain pathologically, although unfortunately not suspected clinically.

**Case 2.** A girl aged 5 years and 9 months, was admitted to hospital on April 24, 1960.

*History.* She developed a cold two days before admission and the next day she began to vomit, but was not ill. On the morning of admission she continued to vomit and became short of breath. She was given 900,000 units of penicillin with no apparent improvement. This shortness of breath became progressively worse throughout the day and by 6.25 p.m. she was admitted to the hospital in a state of severe pulmonary oedema.

**Previous Illnesses.** She was alleged to have had vomiting episodes previously, sometimes associated with shortness of breath. The real nature of these attacks is unknown, but they were never severe nor incapacitating and certainly never as severe as the present episode.

**Family History.** Two aunts had had rheumatic fever and there was asthma in her mother's family.

Examination revealed a restless child, grossly dyspnoeic and cyanosed with cold extremities; temperature 99° F.; examination of heart showed apex beat in the fifth intercostal space just outside the mid-clavicular line. Heart sounds were rapid with a gallop rhythm. The blood pressure was 120/90 mm. Hg in spite of the collapsed state of the child. Pulsus alternans was noted. The radial pulses had poor volume and the jugular venous pressure was not elevated. No hepatomegaly or peripheral oedema were noted. Coarse bubbling râles were found throughout both lung fields. Chest radiograph showed an enlarged heart with widespread pulmonary opacities.

Intravenous cannulation was instituted to facilitate intravenous therapy. Vigorous attempts at resuscitation were made with the administration of digoxin, aminophyllin, hydrocortisone, erythrocine, chloramphenicol, mersalyl and paraldehyde. Oxygen was administered continuously. From admission until death, five and a half hours later, there was a steady deterioration. Morphine sulphate gr. 1/6 was given intravenously in an attempt to control the pulmonary oedema, but with little effect. Vigorous attempts were made to clear her airway with intubation and suction, and positive pressure ventilation was attempted in an endeavour to improve oxygenation and control the oedema. Her upper airway was cleared temporarily only and she steadily became more anoxic. She became unconscious with blood-stained frothy fluid pouring out of the upper respiratory passages and died.

Unfortunately, it was not possible, owing to her desperate condition, to collect any urine, but in view of the similarity to the first case, the diagnosis of acute nephritis was suspected.

**Autopsy.** (PM 26/60 A.C.H.)

**PLEURAL CAVITIES.** Each contained approximately 40 ml. of clear yellow fluid. Pericardial cavity contained 35 ml. of clear yellow fluid. There was frothy blood-stained mucus in the upper respiratory tract, trachea and bronchi. The tracheobronchial lymph nodes were enlarged. Both lungs were heavy and purplish. On incision all lobes were fleshy with blood-stained watery fluid pouring freely from the cut surfaces. Right-sided chambers of the heart were dilated. The ventricular wall was hypertrophied and measured 14 mm. in thickness. In each kidney the capsules stripped easily; the cortex was pale, medullary rays were not visible. The pyramids were dark and congested and the pelves normal.

**BIOCHEMICAL ESTIMATIONS.** Blood urea nitrogen: 60 mg./100 ml.; blood sugar: 80 mg./100 ml.; urine contained albumin +; a blood culture was negative.

**MICROSCOPIC EXAMINATION.** Scattered throughout the lungs were focal areas of bronchiolitis (Figs. 3 and 4).

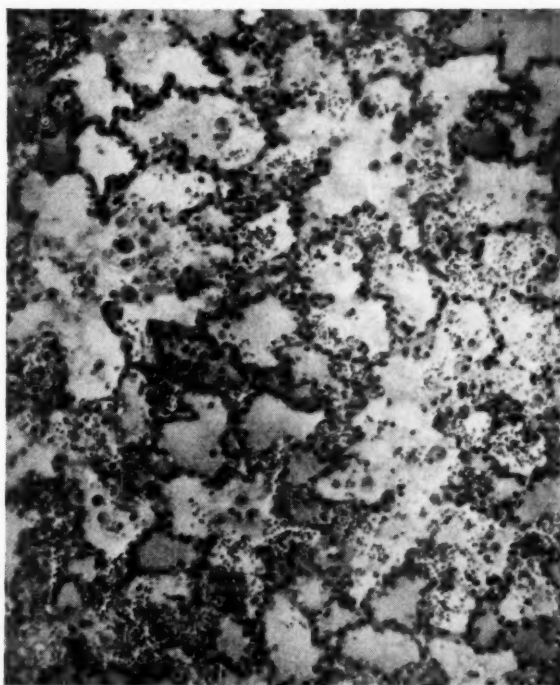
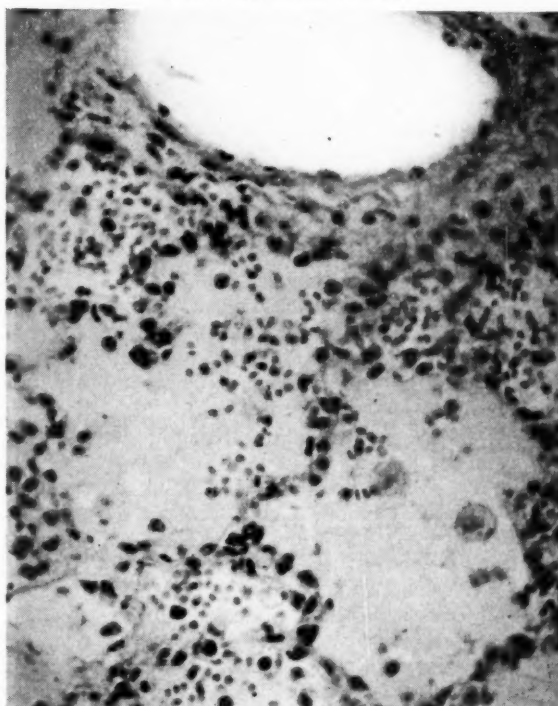


FIG. 3.—(H. and E.  $\times 85$ .)

Both are sections of the lung, Fig. 4 being at a higher power than Fig. 3. The alveoli are filled with oedema fluid containing red blood cells and a few macrophages.

FIG. 4.—(H. and E.  $\times 296$ .)



Other areas showed pulmonary oedema and intra-alveolar haemorrhages. The alveolar walls were congested. Muscular hypertrophy and mild fatty changes were found in the heart. There were diffuse glomerular changes which included avascularity, cellular proliferation, leucocytic infiltration and 'hyaline thrombi' formation in the kidneys. There were no changes in the tubules, vessels or interstitial tissue.

In summary the autopsy showed a female child with acute pulmonary oedema, congestive cardiac failure, hypertrophied left ventricle and diffuse glomerular changes.

The primary cause of death was acute nephritis; the immediate cause, pulmonary oedema.

*Comment.* Throat swabs were collected from other members of the family and in one brother haemolytic streptococci were cultured and he was subsequently treated for this.

The intravenous morphia in this case did not seem to help the child from left ventricular failure, a fact which is unusual in pulmonary oedema. She became more comatose and did not regain consciousness after the injection. There was no elevation of the jugular venous pressure noted in this child. Possibly she was *in extremis* before she was examined and this sign, which is always difficult to assess in children, was not present. The blood pressure was 120/90 mm. Hg at a time when the child was desperately ill and in peripheral circulatory failure with a virtually absent radial pulse. This may suggest that the pressure had been previously higher, but we do not know.

These two cases show many points of similarity and demonstrate several interesting features. In both cases there was a history of an upper respiratory tract infection before the onset of the fatal pulmonary oedema. The significance of this is uncertain as in only one member of the family of Case 2 was a haemolytic streptococcus found. Both cases had been given penicillin injections before admission and both were alleged to have been in good health before the onset of this illness. It would have been valuable to have access to a recent medical examination or a urine test to be certain of this point. Abdominal pain was a feature of Case 1, whereas vomiting attacks had occurred in Case 2. The cause of the abdominal pain and vomiting episodes must remain uncertain. However, it is not impossible that these attacks represented minor episodes of pulmonary oedema, possibly with pleural involvement giving rise to pain.

The degree of hypertension was minimal in both cases. However, the presence of a recordable blood pressure in Case 2 in spite of other evidence of circulatory failure did suggest the possibility of antecedent hypertension. Certainly in each case the hypertension alone was insufficient to lead to cardiac failure and pulmonary oedema (Wood, 1956).

The diagnostic difficulties must also be stressed. In each case in spite of a temperature of 99° F. a diagnosis of a severe bronchopneumonia was made. There were no clinical features to suggest acute nephritis nor other

evidence of cardiac failure. Hypertension was no a feature of either case and we had no urine findings to assist in the diagnosis. The chest radiograph was most helpful in each case and showed the features of pulmonary oedema before the final stage of coughing up salmon-coloured sputum occurred. Thus early diagnosis of this condition is difficult and it seems that once the pulmonary oedema is established no treatment at present available is of any value.

Case 3 represents another recent case of nephritis and pulmonary oedema in whom the features of cardiac failure were more definite.

**Case 3.** The patient was a male aged 1 year and 10 months, who, four days after a supposed attack of bronchopneumonia and otitis media, complained of abdominal pain. He was treated with penicillin for his pneumonia which resolved rapidly and he appeared quite well until the onset of the upper abdominal pain. On admission to hospital he was slightly cyanosed with grunting respirations. Temperature was normal. There were coarse râles over both lung fields. The liver was palpable two fingers below the right costal margin and the jugular venous pressure was raised. A chest radiograph revealed an enlarged heart with small bilateral pleural effusions. In spite of therapy he died 24 hours after admission.

*Autopsy.* (PM 58/57 A.C.H.) The heart was grossly hypertrophied; the lungs were a dull violet colour, firm and did not collapse; and there was much frothy fluid exudate from the cut surfaces. Moderate enlargement of the hilar lymph nodes was noted. Much frothy fluid also was found in the trachea and main bronchi. The cut surfaces of the kidneys were pale.

**HISTOLOGICAL EXAMINATION.** There was congestion of the capillaries of both lungs and much oedema of the alveoli with lamination of a precipitated protein-containing exudate. Polymorphonuclear leucocytes were found in focal patches in the alveolar spaces.

The heart muscle showed hypertrophy of the muscle fibres of both ventricles.

The glomeruli in the kidneys were large, bloodless and hypercellular. Some showed an increase in eosinophilic material with a few polymorphs. There was an occasional cast containing polymorphs in the tubules with some hyaline droplet formation in the tubular epithelial cells.

In summary: acute nephritis with hypertrophy and dilatation of the heart with oedema of the lungs. The cause of death was thought to be due to cardiac failure occurring during the course of an acute glomerulonephritis.

*Comment.* This case, both clinically and pathologically, appears similar to the previous two cases. However, the features of cardiac failure with a grossly hypertrophied and dilated heart were more obvious. The jugular venous pressure was elevated. As in the first two cases, there were no urine findings, a respiratory tract infection appeared to be the precipitating cause of

the nephritis and penicillin was the drug used to treat the pneumonia. In retrospect the pneumonia could have been a mild episode of pulmonary oedema possibly complicated by some infection. There were, however, a few leucocytes in the alveolar spaces.

### Pathogenesis of Pulmonary Oedema

In a discussion on the pathogenesis of pulmonary oedema it is convenient to consider a number of causes (Barach, Martin and Eckman, 1938).

- (1) Left ventricular heart failure;
- (2) Increased capillary permeability;
- (3) Alteration in pressures within the lung:
  - (a) a persistently high intrathoracic negative pressure
  - (b) an abrupt termination of backward pressure against the pulmonary capillaries.

In such conditions as tracheal stenosis the heightened intrathoracic negative pressure may encourage pulmonary oedema. Increased blood flow through the lungs under these conditions and possibly some degree of anoxic damage to the alveolar epithelium may increase capillary permeability and so lead to further pulmonary oedema. Sometimes with the performance of a tracheotomy the sudden change of pressure within the chest may lead to pulmonary oedema. However, the two common causes are left ventricular heart failure and increased capillary permeability from a multitude of causes.

Pulmonary oedema has been reported as occurring in many conditions, and in each an explanation is difficult to find. The occurrence of pulmonary oedema during salicylate therapy was reported by Reid, Watson and Sproull (1950) and a further case was reported by Sutcliffe (1955). More recently Granville-Grossman and Sergeant (1960) reported cases of pulmonary oedema due to salicylate intoxication. In these cases the explanation appeared to be the hypernatraemia that arises in conjunction with over-hydration during treatment. However, the comparative rarity of the condition, the low dosage of salicylate sometimes used and the absence of signs of salicylate intoxication suggest a sensitivity reaction to salicylate in some cases. Acute pulmonary oedema has been seen in cases of hypoglycaemic coma (Weber and Blum, 1942), epileptic fits (Ohlmacher, 1910) and numerous other central nervous system conditions. Cerebral wounds seen during World War I in soldiers were occasionally complicated by pulmonary oedema (Moutier, 1918). The Arnold-Chiari malformation has terminated in pulmonary oedema. Experimental pharmacology has favoured the vagus nerve as a cause of these effects. Stimulation of the efferent path of the vagus

leads to vasodilatation of the lung capillaries and congestion with ultimate transudation of fluid into the alveoli. The suggestion is that cerebral oedema following hypoglycaemic coma, epileptic fits, etc. leads to irritation of the vagus nerve with consequent pulmonary oedema (Weber and Blum, 1942).

Many explanations have been given for the pulmonary lesions in acute rheumatism (Hadfield, 1938; *Brit. med. J.*, 1955). The signs of left lower lobar consolidation previously ascribed to a spreading rheumatic process are now known to be due to lobar compression by pericardial effusion. The abrupt pleurisy sometimes seen is thought to be due usually to pulmonary infarction. It is felt now that cardiac failure is the reason for the congestive changes seen in the lung in acute rheumatic fever. There is, however, a group in which this does not apply, and in a few of these, pulmonary oedema due to salicylates may be the explanation. Similar lesions to those seen in rheumatic fever have been demonstrated in a sulphonamide sensitivity (French, 1946), and still others have been produced experimentally in rabbits sensitized to egg-white protein (Cannon, Walsh and Marshall, 1941). Undoubtedly, pulmonary oedema can be produced by these sensitizing reactions.

Pulmonary oedema to a greater or lesser degree is comparatively common in pneumonia. In these cases an increase in capillary permeability as a result of the infection may be the cause. When the oedema is the main pathological feature these cases may be indistinguishable clinically from the three cases described when they present suddenly, and rapidly become asphyxiated and die. We have recently seen two such cases in girls in our hospital. In neither case were the lesions of acute nephritis to be seen in the kidney.

### Pulmonary Oedema in Relation to Renal Disease

The first report in Australian literature of pulmonary oedema in association with renal disease was given by White (1907), who described the clinical record of a case of acute suffocative pulmonary oedema in a male of 25 years, who had had several episodes of pulmonary oedema associated with hypertension and cardiac failure. He also had the clinical features of nephritis with some oedema and albumin in the urine. This case was undoubtedly one of congestive cardiac failure with a large heart, triple rhythm and hypertension. Both morphine and venesection improved the patient on several occasions.

Stanton and Tange (1958) have described nine cases of the combination of pulmonary haemorrhage

and glomerulonephritis. They mention 12 other cases from the literature, but suggest that this does not, in all probability, reflect its real frequency. They suggest the term Goodpasture's syndrome for the condition of glomerulonephritis complicated by severe idiopathic pulmonary haemorrhage. Goodpasture (1919) described a case during the influenza epidemic of that year with this combination of lesions and felt that they were an unusual manifestation of influenza. Stanton and Tange's cases are a little different from ours in that they persisted with haemoptyses for several weeks or months before the final episode overtook the patients. The final episode, however, was of sudden onset with breathlessness and features of pulmonary oedema very similar to our cases. These authors state that the most acute cases of this syndrome may be clinically indistinguishable from cases of glomerulonephritis complicated by severe bronchopneumonia. They mention two cases aged 25 years and 8 years who died suddenly and in whom a chest radiograph showed bilateral diffuse pulmonary lesions; at autopsy the lungs showed oedema fluid with red cells in the alveoli, but also many polymorphs as well. Our cases showed a few polymorphs in the alveolar exudate similar to these two cases and it is difficult to be certain what part infection played in the illness of these patients. Another feature of their nine cases was the fact that the average age was 25 years. It appears, therefore, to be a disease of young adults.

More recently from Manchester a report of 65 cases of acute nephritis in whom 37 showed radiologically detectable lung lesions was given by Holzel and Fawcitt (1960). The majority fell into the school age and the authors stated 'It seems puzzling, however, that the typical picture of pulmonary oedema was seen in only two out of 37 cases with pulmonary lesions.' The other 35 cases showed partial collapse, consolidation, interlobar and pleural effusions. All were seen at the onset of the illness in the hydraemic stage, and spontaneous and rapid resolution occurred after the onset of the diuresis. These facts prompted the authors to postulate that these lung lesions were due to the accumulation of oedema fluid itself and were probably not inflammatory in origin nor due to cardiac failure. The reason given for the accumulation of the oedema fluid, however, was not entirely convincing.

#### Theories of Pathogenesis in Relation to Our Cases

In the three cases described the features of pulmonary oedema were found in association with lesions in the kidney glomeruli such as are found

in acute glomerulonephritis. It is reasonable, therefore, to assume that acute nephritis should be the primary diagnosis and that both the lung and kidney lesions should be part of the same disease process. The mechanism of the changes in the lungs is difficult to explain. The mechanism causing the pulmonary oedema in these cases is said to be due to acute left ventricular heart failure (Wood, 1956). The onset in these cases was extraordinarily rapid, and in the absence of other signs of heart failure either clinically or at autopsy, this explanation seems unlikely. However, the presence of left ventricular hypertrophy at autopsy in each of two cases is an interesting feature and needs explanation. Hypertrophy of cardiac muscle suggests that the disease process may not have been as sudden as would appear clinically. Unfortunately, we know nothing of the children before the terminal illness, so it is possible that a smouldering nephritis could have been present. This appears unlikely, as in each case the parents were quite definite that the child was well before the terminal illness; also the microscopic kidney changes are those of a recent event and not those of a smouldering nephritis. However, it is well known that hypertrophy of the cardiac muscle may appear quite quickly in children.

In the early stages of acute nephritis there is a considerable reduction in the glomerular filtration rate due to resistance in the glomerular arterioles (Black, Platt, Rowlands and Varley, 1948). This, combined with relatively normal tubular function, leads to sodium retention and consequently an increase in circulating blood volume. Cardiac enlargement, pulmonary oedema and cerebral oedema are all complications of sodium retention (Rosenheim, 1951). In view of the increase in circulating blood volume, one expects a rise in jugular venous pressure and the presence of peripheral oedema in these cases. In actual fact in neither of the first two cases was a raised jugular venous pressure recorded and peripheral oedema was carefully searched for but not found. In no case was the liver enlarged and the pulse rate was slow and regular in each case. The heart was not enlarged clinically and no abnormality was noticed on auscultation. Unfortunately, no biochemical tests were performed before death; nevertheless, these inconsistencies seem hard to reconcile with the sodium retention and increased plasma volume hypothesis.

Pulmonary oedema is known to occur in uraemia (Doniach, 1947), and the interstitial pulmonary oedema in the so-called uraemic lung was considered as an explanation in the first two cases of acute

nephritis. In the first case the blood urea nitrogen was 22 mg./100 ml. and in the second was 60 mg./100 ml. However, neither of these are high enough to invoke uraemia as the mechanism.

Another condition to be considered in the differential diagnosis in which renal and pulmonary lesions occur is polyarteritis with lung involvement as described by Rose and Spencer (1957). Nasal granulomata or granulomatous lesions in the respiratory tract were a feature (Wegener's granulomatosis). Peripheral arterial lesions and eosinophilia are also features of this disease. None of these were found in our cases and it was felt, therefore, that polyarteritis was unlikely as a diagnosis. Histopathological examination supported this clinical impression.

The roentgenological manifestations of pulmonary oedema have been described (Nessa and Rigler, 1941). They are non-specific as far as the aetiology is concerned and are subject to a wide range of variation. The physical findings are often minimal in the presence of extensive radiographic findings, so that a chest radiograph is invaluable in early diagnosis. The classical description of the chest radiograph is of butterfly-shaped symmetrical chest opacities with greatest density at the hilum and fading towards the periphery, leaving the apices and bases clear. The opacity has a homogeneous appearance and obliterates all lung detail. However, there are well-recognized variations in which the opacity has a fine irregular stippled appearance; it may be unilateral or even localized to one area of the lung, i.e. pneumonia complicated by pulmonary oedema.

The radiological appearances of the oedema of the lungs may be caused by many other disease processes. Similarly, the pathology described in these various situations may represent various stages of one causal process.

#### Hypothesis

It seems that none of the explanations offered is entirely satisfactory. At the risk of adding another, perhaps an aetiology based on an allergic mechanism has much to recommend it.

It appears that in each case the onset of the upper respiratory tract infection triggered off the fatal mechanism whatever it was. Case 1 had a cold one week before admission, Case 2 two days before admission, and Case 3 a pneumonia. The relation between a haemolytic streptococcal throat infection and development of acute nephritis is well known. It is thought that it is a reaction due to hypersensitivity to the infecting organisms. Therefore, it is reasonable to look for an explanation of the lung pathology along these lines also.

Although no haemolytic streptococci were isolated from the throats of either of the cases, in one brother of Case 2 the organisms were found. He had an upper respiratory tract infection at this time and was subsequently treated with penicillin.

It is tentatively suggested, therefore, that the haemolytic streptococcus may be the causal agent of the disease. The products of infection by this organism lead to the lesions of acute nephritis on the one hand and pulmonary oedema on the other. It is possible that there are all grades of this reaction, our first two cases representing the severe reaction with the accent on the lung, giving rise to rapidly fatal pulmonary oedema. Neither of these cases responded in any way to cortisone, but it was felt that the process was too well advanced for steroids to make any difference.

In the first case a penicillin allergy was considered in the diagnosis. It was thought, however, that the time relation and the type of reaction were unlike the reactions that are due to penicillin allergy. There were no skin lesions. No other allergens seemed to suggest themselves in either case, although Case 2 had a family history of allergy.

The pulmonary lesions in these cases bear a close resemblance to those described in rheumatic fever (Hadfield, 1938; Naish, 1928). This similarity perhaps supports a hypersensitivity reaction as the explanation, as also does the rapidity of onset of the reaction itself. As in rheumatic pneumonia, a relatively high proportion of the lung needs to be involved before symptoms appear. It is quite possible that the pathology is of much slower onset than appears clinically and only when the extent to which the lung is involved reaches a critical level do severe symptoms develop.

#### Treatment

Treatment in our three cases was disappointing. It has been suggested, many years ago, that positive pressure within the lungs would be of great assistance in the treatment of pulmonary oedema. This whole subject is well reviewed by Barach *et al.* (1938), who describe experimental work and the successful clinical use in eight cases of positive pressure respiration. They maintain that positive pressure within the alveoli decreases the amount of blood entering the right heart and in that way diminishes pulmonary congestion and facilitates the clearing of pulmonary oedema, and the direct opposing physical force on the external capillary wall tends to counteract any tendency to ooze serum.

In Case 2 positive pressure was tried as a method of treatment. It was not successful and presented

practical difficulties in the conscious anoxic patient and is probably too late in the unconscious patient in any case. However, it offers the only positive approach that we have at present, and we are therefore persisting with its use.

As acute nephritis is a disease with a good prognosis in most cases, it appears that if some method were available for getting these children over this attack of pulmonary oedema the renal lesion would, in all probability, heal. It is hoped that this report may stimulate others to make further inquiries in this field in the hope of being able to find an answer to this problem.

The purpose of this report is to bring notice to bear on this condition of acute suffocative pulmonary oedema and to stress the importance of taking the blood pressure and examining the urine in any suspected case. Shortness of breath in any case following an upper respiratory tract infection is usually due to the onset of pneumonia. However, the knowledge that this condition begins in a similar fashion may help in early diagnosis.

### Summary

Three fatal cases of acute nephritis leading to pulmonary oedema are described. An account of the pulmonary lesions is given and the possible mechanisms involved are discussed. The difficulties in diagnosis and treatment are stressed. A possible role of the haemolytic streptococcus in causing a sensitivity reaction affecting both lungs and kidneys is put forward as the most satisfactory explanation of the clinico-pathological findings. An increased awareness of the clinical condition may lead to early diagnosis and also to more work in this field which is long overdue and thence to some form of effective therapy for this distressing fatal condition.

I wish to thank the Board and Members of the Honorary Staff of the Adelaide Children's Hospital (Inc.) for permission to publish these cases. I am indebted to Dr. M. C. Fowler of the Pathology Department for the use of the pathological material, and to Mr. Ray Boyd for the preparation of the illustrations. I am grateful to Dr. M. Innis for his helpful comments in the preparation of the paper, and I wish to thank Miss U. Pridham for her help in typing this paper.

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# ISONIAZID IN PRIMARY TUBERCULOSIS IN INFANCY\*

## A CONTROLLED CLINICAL TRIAL

BY

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Before the introduction of isoniazid it had been established that streptomycin was of little use in the treatment of primary tuberculosis. It did not prevent extension of the primary lesion within the lung (Lorber, 1950), and it did not prevent the occurrence of haematogenous spread or of meningitis during treatment.

When isoniazid became available it seemed essential to establish its value, if any, in the treatment of uncomplicated primary tuberculosis. As the prognosis of primary tuberculosis in English children is generally favourable, it was clear that a strictly controlled trial would be necessary to reach satisfactory conclusions. It was also clear that infants were the most suitable subjects for inclusion in such a trial, because one could be reasonably certain that the infection was of recent onset, and because in infants tuberculous infection much more commonly results in tuberculous illness than in older children. The study of a relatively small group of patients would, therefore, be sufficient to determine the value, if any, of a proposed line of treatment.

Treatment of primary tuberculosis with isoniazid might influence the course of the disease in four different ways:

- (1) it could influence the course of the primary tuberculosis itself;
- (2) it could eliminate local spread and local complications, e.g. collapse, obstructive emphysema or bronchiectasis;
- (3) it could prevent haematogenous dissemination, miliary tuberculosis and tuberculous meningitis; and
- (4) it could prevent post-primary pulmonary tuberculosis.

It will take many years of observation to reach conclusions on the last point, but it is possible to determine in a much shorter time the effect of isoniazid on the course of the primary tuberculosis

itself and its value in the prevention of the immediate post-primary complications.

### Present Trial

A prospective trial was designed to answer these problems. This paper is concerned with the results obtained after five years of observation. Past experience with tuberculous infants suggested that it was ethically justifiable to withhold specific treatment from infants with uncomplicated primary tuberculosis as long as they were under strict supervision. Under these conditions any complication could be detected and treated early with an assurance of a satisfactory recovery.

**Plan and Method of Analysis.** The trial began in April 1952, when isoniazid became available. All tuberculin positive infants aged 24 months or less with uncomplicated and previously untreated primary tuberculosis were enrolled in the trial. The large majority of infants who were enrolled in the investigation were first seen at a Tuberculosis Contact Clinic because they had been in contact with a known case of tuberculosis. A few had been admitted to hospital for various reasons and were found to have primary tuberculosis. Once an infant satisfied the criteria for inclusion in the investigation, he was allocated by random sampling into one of two groups (Table 1). Patients in the first group ('treated cases') received isoniazid (5 mg./kg. daily), and P.A.S. (0.5 g./kg. daily) in three divided doses. No injections were given. Treatment was given for three months. Patients in the second group ('controls') received no specific treatment. Children in both groups received the same vitamin supplements. The protocol of the investigation provided that if any patient were to develop tuberculous disease which required specific treatment, such treatment was to be given by isoniazid, streptomycin or any other suitable drug.

The trial was to be run on a basis of domiciliary

\* Based on a paper delivered at the Children's Hospital Medical Centre, Boston, Mass., in January 1961.

TABLE 1  
PLAN AND METHOD OF INVESTIGATION

<i>Criteria for inclusion:</i> all tuberculin positive infants age 24 months or less with uncomplicated primary tuberculozes		
<i>Method of allocation:</i> random sampling		
<i>Method of initial investigation and follow-up:</i>		
<i>Treatment</i>	<i>Treated</i> Isoniazid 5 mg./kg. daily and P.A.S. 0.5 g./kg. daily for 3 months  Vitamin supplements	<i>Controls</i>  Vitamin supplements only
<i>Additional treatment</i>	as required	
<i>Hospital admission</i>	exceptional	

TABLE 2  
SEX INCIDENCE AND AGE ON ADMISSION TO TRIAL

Age (mths)	Treated	Controls
0-6	2	5
7-12	7	9
13-18	10	10
19-24	11	5
Average age (mths) ..	16	13
Boys .. .. .	15	17
Girls .. .. .	15	12

TABLE 3  
PRINCIPAL SOURCES OF INFECTION  
AND THEIR FATE

Source of Infection	Last Known Condition			Total
	Died	Still Active	Quiescent	
Mother .. ..	4	5	7	16
Father .. ..	6	3	14	23
Grandparents ..	2	3	3	8
Other relatives ..	2	2	5	9
Neighbours .. ..	1	0	0	1
All known sources ..	15	13	29	57

management. The large majority of the patients were not admitted to hospital except for a few days of initial clinical and bacteriological studies. Exceptionally infants were admitted for longer periods either because there was no one to look after them at home, or because they developed complications. Clinical and radiological examinations were performed in both groups at monthly intervals in the first four months; at intervals of two months up to the end of the first year, and then at three-, four- and six-month intervals up to the

end of the second, third, fourth, and fifth years respectively. More frequent examinations were performed when necessary. It was fortunate that a 100% follow-up was secured. A few infants left the district, but either attended at the appropriate time for examination even from long distances, or else attended Chest Clinics in their new areas. Information about these was then obtained from the chest physicians concerned.

**Material and Clinical Features on Admission.** Between April 1952 and October 1955, 59 infants (32 boys and 27 girls) were admitted to the investigation. Thirty were allocated into the group treated with isoniazid plus P.A.S., and 29 received no specific therapy at this stage ('controls'). In order to safeguard the infants in the control group, and to determine the necessary length of the investigation, concurrent analyses of the results were carried out. The investigation, therefore, could have been interrupted at any time if evidence accumulated that the treated group fared better than the controls. The investigation was concluded in October 1960. At this stage all patients had been observed for five years. Events after the fifth anniversary of the inclusion in the trial will not be considered in this paper.

The control group was accidentally weighted with small infants. On admission the average age of the treated infants was 16 months, and of the controls 13 months. There were two treated infants aged 6 months or less as compared with five controls (Table 2). Nine treated infants had a chronic cough on admission, and five of these had some degree of stridor. Six controls had a chronic cough, but only one had stridor. With regard to symptoms, therefore, the treated group was weighted with more severe cases, and this feature helped to counteract the influence of age in the opposite direction. Four treated infants and six controls showed tuberculin conversion in the two months immediately preceding their inclusion in the trial.

**Contact History.** A human source of infection was either known on admission or became known as a result of contact investigations in 29 of the treated and in 28 of the controls. They were mostly members of their own household, and usually they were close relatives (Table 3). The only two infants whose source of infection was not found both had primary abdominal complexes. This became apparent later when calcified mesenteric lymph nodes were demonstrated radiologically.

The principal source of infection was the mother in 16, the father in 23, a grandparent in eight,

another relative in nine and a neighbour in one. In several instances multiple sources of infection were found, but in Table 3 only the principal source is shown. These sources of infection had usually a severe disease, as shown by their subsequent progress: 15 died during the period of observation; 13 had active disease at the end of the five-year period of observation, and were still undergoing treatment. Only 29 were considered to be in the quiescent stage.

**Radiological Features on Admission.** The radiological changes in the lungs on admission are shown in Table 4. The distribution and the types of the lesions were very similar in the two groups. Twenty-one treated infants and 22 controls had radiologically demonstrable lung lesions at the first examination. Thirty-one of these infants had gross lesions.

#### Results: Clinical Course

The course of the disease was uneventful in most infants. There were no deaths either from tuberculosis or from any other causes. Twenty-five treated children and 24 controls had no tuberculous illnesses during the period of observation (Table 5).

#### Tuberculous Illnesses

**Treated Cases.** Five children who had been treated with isoniazid and P.A.S. had tuberculous illnesses at some stage. In two the illness was already present on admission into the investigation. These two (Cases 1 and 2) strictly speaking should not have been included in the investigation. In one infant the illness developed during isoniazid treatment (Case 3), and in two it occurred after the conclusion of the routine treatment (Cases 4 and 5). Only one child required additional antibiotic chemotherapy.

**CASE 1 (M.N., Table 10).** This girl was 22 months old when she was admitted to the investigation. At this stage she had stridor associated with obstructive emphysema of the left lung (Fig. 1). The stridor became more severe while on treatment and bronchoscopy had to be performed two weeks after admission. Although no obstruction was seen, her condition rapidly improved after bronchoscopy. She lost her stridor and made an uneventful recovery.

**CASE 2 (K.S., Table 8).** This boy was 11 months old on admission. His mother was in a sanatorium at the time he was brought to the clinic by a neighbour. They were unaware that the child had any subjective complaint. The baby was difficult during examination, but limitation of movement of the left shoulder joint was noted. As there was no swelling, tenderness or wasting and a

TABLE 4  
RADIOLOGICAL FEATURES IN LUNGS ON  
ADMISSION

Radiological Features	Treated	Controls
Negative .. .. .	9	8
Hilar glandular enlargement only ..	4	7
Gross lesions .. .. .	17	14
Segmental or lobar .. .. .	7	6
Big or multiple opacities .. .. .	9	6
Tuberculoma .. .. .	1	2
Total .. .. .	30	29

TABLE 5  
TUBERCULOUS ILLNESSES

Illness	Treated		Controls	
	First Three Months	Later	First Three Months	Later
Meningitis .. .. .	—	—	1	—
Miliary .. .. .	—	1	—	—
Bronchial obstruction .. .. .	2	—	1	—
Bronchial spread .. .. .	—	1	—	1*
Osteitis .. .. .	1†	—	—	—
Soft tissue abscess .. .. .	—	—	1†	—
Phlyctenular conjunctivitis .. .. .	—	—	1*	2

\* These developed while receiving isoniazid and streptomycin.

† Present, but unrecognized on admission.

radiograph of the humerus and shoulder joint was normal, not enough importance was attached to the limitation of movement. Later it transpired that the mother had noticed stiffness of his left shoulder for several weeks past. Subsequently the typical changes of tuberculosis of the left shoulder joint and of the upper end of the humerus were radiologically demonstrated. Five years later this child was quite well, but he had ankylosis of his left shoulder joint. This is the only

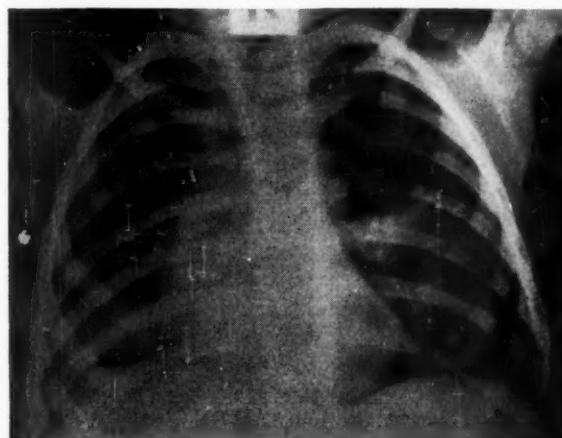


Fig. 1.—Case 1: Obstructive emphysema of the left lung due to tuberculous glands in the left hilum.

child in the whole series of 59 who has subjective residual disability from his tuberculous infection. It is clear in retrospect that he already had tuberculosis of his shoulder joint on admission and should not have been included in the investigation. His management, nevertheless, would have been very similar.

**CASE 3 (G.E., Table 10).** This girl was 20 months old and symptom-free on admission. She developed acute bronchial obstruction during treatment, with gross cyanosis. An emergency bronchoscopy had to be carried out, which saved her from suffocation. Much tuberculous granulation tissue was removed from her bronchi. She then made an uneventful recovery and remained symptom-free during the next five years. A very small, well-defined calcified complex in the right lower lobe and the right hilum is the only residual evidence of her past illness.

**CASE 4 (P.C., Table 8).** This boy of 24 months of age remained symptom-free during chemotherapy and for nine months afterwards. Then he developed an acute febrile respiratory illness which persisted for several weeks. This illness was attributed to a massive collapse of the right middle lobe which occurred as a result of bronchial obstruction by a group of calcified glands. Subsequently he remained symptom-free for the remainder of the five-year period of observation (Figs. 2 and 3).

The following is a case of miliary tuberculosis.

**CASE 5 (B.F., Table 8).** This girl was 8 months old on admission. She was symptom-free and had an uncomplicated primary complex in her right upper lobe. Her progress was uneventful during the three months while she was on treatment. Although she remained well, a routine chest x-ray six months after admission showed that she now had generalized miliary tuberculosis. Tubercle bacilli were recovered from her gastric washings. She was given a six months' course of isoniazid and streptomycin treatment and she made an uneventful recovery. Five years after her admission she was perfectly well and had a calcified complex in her right upper lobe.

**Controls.** Five children who were not given specific treatment on admission developed tuberculous illnesses. In one the illness was probably present on admission but was not recognizable (Case 6), and in two it developed during the first three months of observation (Cases 7 and 8). Two others, whose history will not be described in detail, developed phlyctenular conjunctivitis during the second and third year of observation respectively. Of these five, two required full anti-tuberculous chemotherapy (Cases 6 and 8). All made a complete recovery.

**CASE 6 (E.R., Table 11).** This 11-month-old boy was symptom-free on admission but had an extensive shadow in his left upper lobe which showed incipient central

calcification (Fig. 4). He also had enlarged calcifying cervical glands. A week after admission he developed a swelling over the lower half of his sternum, almost in the mid-line. This later became fluctuant. Neither at this stage nor at any other time was there any clinical or radiological evidence of an underlying bony disease of either the sternum, the ribs or the vertebrae. When the swelling appeared the infant was put on isoniazid and streptomycin treatment and this treatment was given for six months. The soft tissue abscess was incised and tubercle bacilli were cultured from the pus. The abscess healed well. This infant also developed phlyctenular conjunctivitis both during and after the conclusion of his chemotherapy. At the end of five years of observation he was perfectly well, but he had extensive calcifications in his cervical, thoracic and abdominal lymph nodes as well as in his spleen, and he had a persistent segmental collapse in his left upper lobe (Figs. 4-6).

**CASE 7 (S.S., Table 9).** This boy was 4 months old on admission. He developed bronchial obstruction with stridor and general signs of ill health during the first three months of observation. He made a rapid recovery without any active measures being taken, but had several brief episodes of stridor during the first year. He had no subjective symptoms during the next four years. At the end of five years he was perfectly well, but had extensive calcified lesions in both lung fields, in both hila and in the abdomen (Figs. 7-9).

The following is a case of tuberculous meningitis.

**CASE 8 (S.B., Table 9).** This boy was 10 months old on his admission. He was symptom-free but had an extensive recent lesion in his right upper lobe and enlarged glands in the right hilum (Fig. 10). During the first three months of observation he became slightly off colour. For this reason his cerebrospinal fluid was examined. It showed minimal changes characteristic of 'serous tuberculous meningitis' (Lincoln, 1947). Gradually the changes in the cerebrospinal fluid developed into the typical findings of tuberculous meningitis and tubercle bacilli were then recovered on direct smear and also cultured. He was treated with intramuscular and intrathecal streptomycin plus P.A.S. for six months and made an uneventful recovery. He never had any neurological signs. Five years after admission he was perfectly well, had a normal intelligence, normal hearing and a normal electroencephalographic tracing. He had a calcified complex in his right upper lobe (Figs. 10-12).

The infants who developed haematogenous complications were under 12 months of age, and all had gross radiological changes on admission. One treated infant and two controls required anti-tuberculous chemotherapy above that laid down in the plan of the investigation.

**Non-tuberculous illnesses.** The efficiency of chemotherapy, if any, might have shown itself by the improved general health of the infants and a reduced liability to non-tuberculous illnesses. In

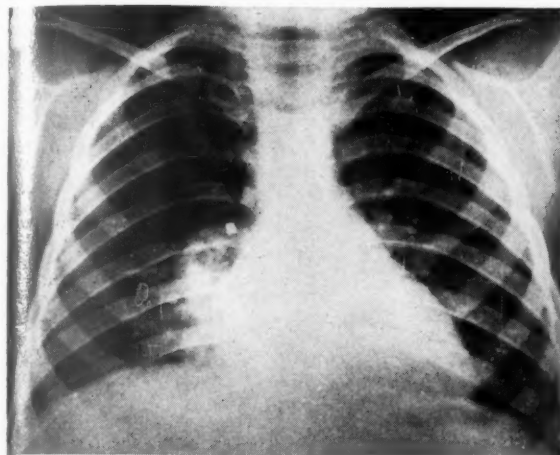


FIG. 2.



FIG. 3.

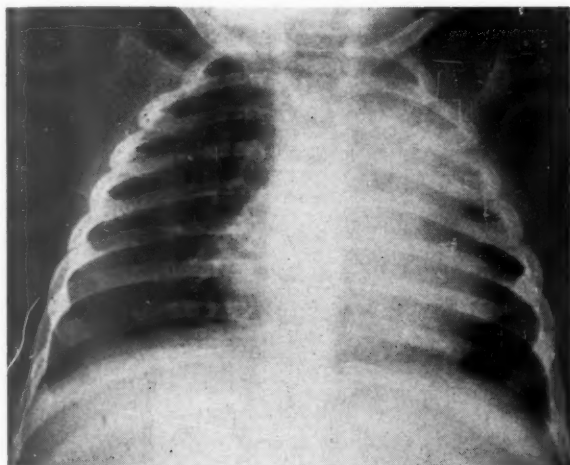


FIG. 4.

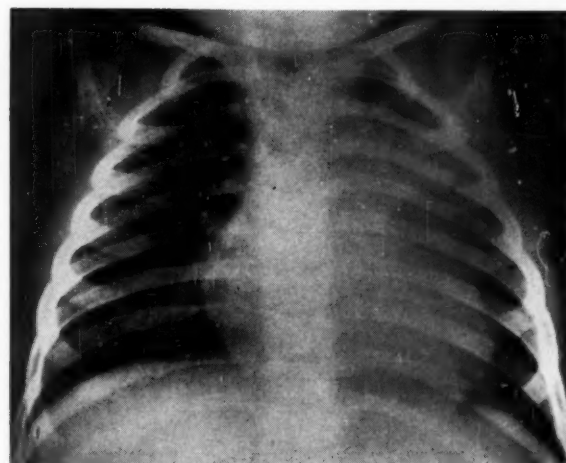


FIG. 5.

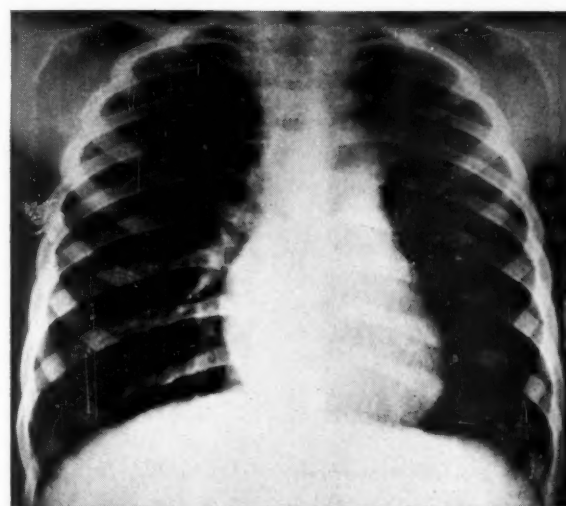


FIG. 6.

FIG. 2.—Case 4 (P.C.) (Table 8): Collapse of right middle lobe one year after admission.

FIG. 3.—Case 4: Bilateral calcified complexes five years later.

FIG. 4.—Case 6 (E.R.) (Table 11): Extensive opacity with faint calcifications, occupying the whole of the left upper lobe, on admission.

FIG. 5.—Case 6: Slight improvement one year later, with persistent segmental collapse.

FIG. 6.—Case 6: Five years later; small segmental collapse persists. There are calcified hilar lymph nodes.

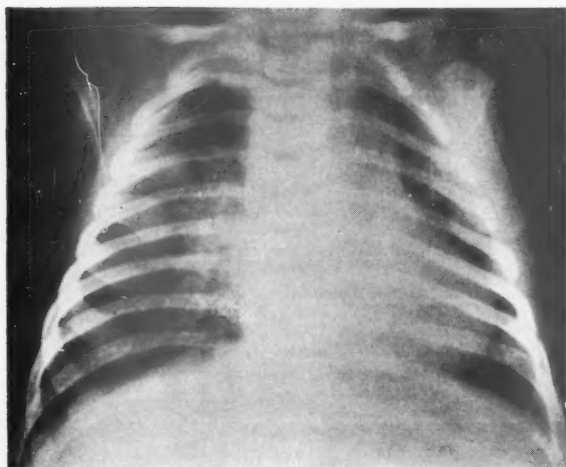


FIG. 7.—Case 7 (S.S.) (Table 9): Large mottled shadows in right mid-zone and hilum, on admission.

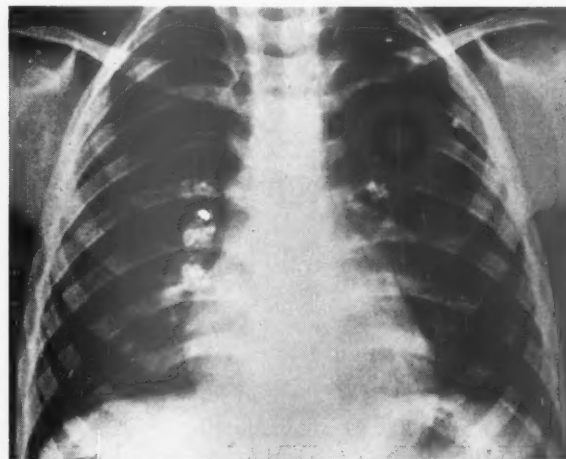


FIG. 9.—Case 7: Bilateral large, dense calcified complexes five years later.

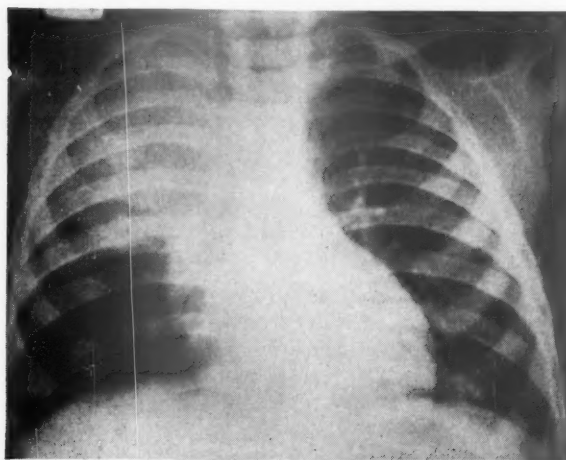


FIG. 11.—Case 8: Much worse one year later. The whole upper lobe is involved.

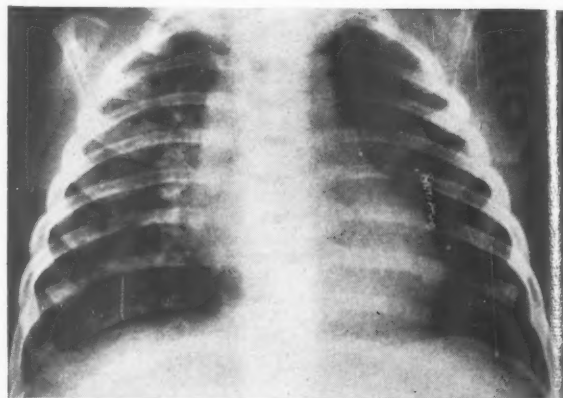


FIG. 8.—Case 7: Increased mottled shadowing in right lung, plus enlargement of the left hilar nodes, and some mottling of the left lung three months later.

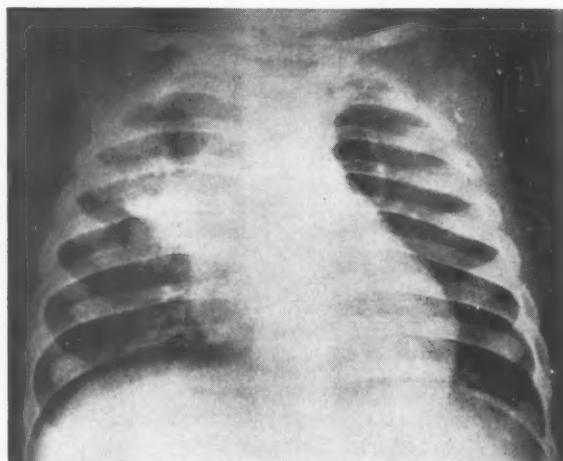


FIG. 10.—Case 8 (S.B.) (Table 9): Extensive recent primary complex in right upper lobe on admission.

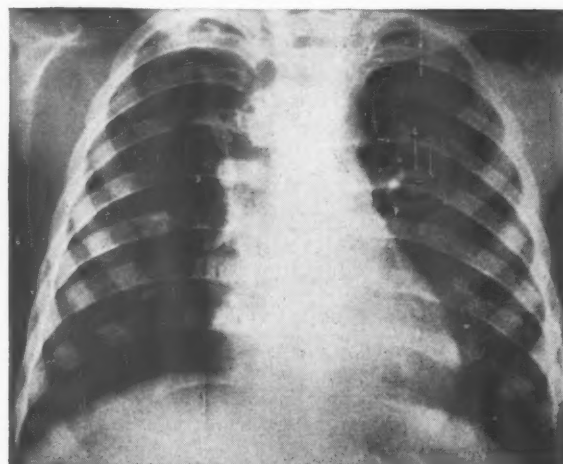


FIG. 12.—Case 8: Large calcified complex in right upper lobe five years after admission.

TABLE 6  
NON-TUBERCULOUS ILLNESSES

Disease	Treated	Controls*
Measles .. .. .	18	13
Pertussis .. .. .	4	6
Upper respiratory infections, including sore throat .. .. .	19	28
Lower respiratory infections .. .. .	14	19
Other illnesses .. .. .	43	35
All illnesses .. .. .	98	101

\* Excluding two patients who were later given chemotherapy.

TABLE 7  
AVERAGE GAIN OF WEIGHT

	Average Weight Gain (kg.)	
	Treated	Controls*
During first 3 months .. .. .	0.8	1.0
At 1 year .. .. .	2.6	2.9
At 2 years .. .. .	4.6	5.0
At 3 years .. .. .	7.4	7.0
At 4 years .. .. .	9.0	8.3
At 5 years .. .. .	10.8	10.7

\* Excluding two patients who were later given chemotherapy.

fact, no significant difference was found between the groups in this respect (Table 6). Not counting common colds, the 30 treated patients had 98 intercurrent illnesses and 27 controls (having excluded two who had to have chemotherapy) had 101 illnesses. The distribution of the illnesses was very similar. Measles was followed by a considerable temporary worsening of the radiographic appearance of the lung lesion in two treated infants. No other child suffered any detectable clinical or radiological exacerbation of his condition following an intercurrent illness.

**Weight Gain.** There was very little difference between the two groups with regard to weight gain either during the initial three-month period or subsequently (Table 7).

**Radiological Changes.** The radiological changes in the lungs which occurred during the period of observation are described below, related to the findings on admission:

- (1) 17 infants whose radiographs appeared normal;
- (2) 11 infants who showed enlarged hilar lymph nodes;
- (3) 31 infants who had gross radiological changes. In each group the changes in the treated children

are described first, separate consideration being given to events during the first three months after admission.

(1) *17 Infants with Negative Radiographs on Admission.* There were 17 infants whose radiographs of the chest were normal on admission. Nine were treated and eight were controls. Three treated infants and four controls developed intrathoracic calcification either of the hilar lymph nodes or of the whole primary complex (Table 13). None of these had a demonstrable active lesion at any time and the calcifications were the first signs of an intrathoracic lesion. The calcifications became visible approximately three years after admission, and were very small. One child in each group had temporary lobar consolidation five months and four years after admission, respectively. These cleared quickly and completely and were not followed by calcification. These lesions were considered to be non-tuberculous.

Seven infants (three treated and four controls) who had no pulmonary lesion at any time, developed calcified mesenteric lymph nodes approximately two years after admission.

In the remaining three infants (all treated) no active or calcified tuberculous lesion was discovered at any time up to five years after their admission. The only evidence of their tuberculous infection was a repeatedly positive tuberculin reaction.

It is seen, therefore, that radiologically the progress of all these 17 infants was uneventful.

(2) *11 Infants with Hilar Glandular Enlargement on Admission.* Eleven infants (four treated and seven controls) on admission presented with unequivocal and often gross hilar enlargement, but without a radiologically demonstrable parenchymal lung lesion. In three of the four treated infants the lesions regressed and calcification took place up to three years after admission. In one treated infant a temporary collapse of the left lower and of the right middle lobe occurred 22 months after admission. This was not associated with any illness, and the collapse was not present two months later. The final picture in all four treated infants was that of a small, single calcified primary complex.

None of the seven children in the control group showed any progressive enlargement of the glands or an extension of the lesions into the lung parenchyma in the acute stage, nor did they develop segmental collapse. On the final radiograph they all had calcified primary complexes. In three these were single and small, in three double primary calcified foci of moderate size were seen in two

different lobes either in the same lung, or in the opposite lung. In the seventh child extensive bilateral calcification developed. This infant had a completely uneventful clinical course.

(3) *31 Infants with Gross Pulmonary Lesions on Admission.* Thirty-one infants had more extensive pulmonary lesions. There were three different types. In 15 infants (nine treated and six controls) the lesions consisted of single or multiple primary complexes in which the pulmonary components were sufficiently large to produce a clearly definable shadow on the radiograph of the chest. In 13 infants (seven treated and six controls) large opacities or translucencies of lobar or segmental distribution were seen and were attributed to consolidation, and/or collapse or to obstructive emphysema. Three infants (one treated and two controls) each had a solitary, very large round parenchymal

lesion without correspondingly large hilar enlargement. These three lesions were considered to be tuberculomas. These 31 infants constitute the most important group. Their radiological changes are described individually, in some detail, together with brief clinical notes in Tables 8-12.

(a) 15 INFANTS WITH LARGE OR MULTIPLE PRIMARY COMPLEXES

*Treated Cases:* There was one infant among the nine treated cases (Table 8) (J.A.) whose lung lesion showed significant deterioration in spite of isoniazid and P.A.S. treatment during the first three months. This deterioration immediately followed an attack of measles (Figs. 13 and 14). In two other children (P.C. and D.C.) deterioration occurred during the months following the conclusion of treatment and one of them (P.C.) had a temporary lobar collapse (Figs. 2 and 3). The most spectacular complica-

TABLE 8  
RADIOLOGICAL PROGRESS IN NINE TREATED INFANTS WITH LARGE OR MULTIPLE PRIMARY COMPLEXES ON ADMISSION

Name	Age O/A (mths)	Radiological Features					Clinical Course
		On Admission	At Three Months	At One Year	Later	Special Features	
P.C.	24	Fresh primary complex right middle lobe, right hilum and focus in left lower lobe	Incipient calcification on right	Much worse; collapse of right middle lobe; calcification progressing (Fig. 2)	Extensive calcified shadows right middle, right lower and left lower lobes and both hila 3-5 yrs (Fig. 3)	Lobar collapse after conclusion of treatment	Uneventful
R.W.	18	Large complex right mid-zone and right hilum; enlarged left hilum	Same	Same	Calcification of both hila and of primary focus in left lower lobe 3-5 yrs	—	Uneventful
S.R.	16	Massive opacities right upper and right middle lobes and grossly enlarged paratracheal glands (Fig. 15)	Right upper lobe lesion and paratracheal glands; much smaller—dense opacity persists in right middle lobe	Minimal shadows in right upper lobe; no other lesions	Normal by 2 yrs; no calcification developed by 5 yrs (Fig. 16)	Remarkable and complete clearing of extensive lesions	Slight intermittent stridor during first year
M.M.	10	Several opacities in left upper lobe; enlargement left hilum; early calcification	Much clearer; several calcifying shadows left upper lobe, left lingula and left hilum	Progressive calcifications	Dense calcified lesion at 2 years with progressive absorption up to 5 years	Final radiograph virtually normal	Uneventful
D.C.	9	Very large right upper lobe and right mediastinal complex	Slight improvement	Mass increasing in size; central calcification	Gradual calcification ending up with small calcified complex 3-5 years	—	Uneventful
J.A.	20	Ill-defined shadows left lung and primary complex left lower lobe with early calcification (Fig. 13)	Much worse—gross opacity of entire left upper lobe (Fig. 14)	Well calcified complex left upper lobe and left hilum	Gradual calcification resulting in small calcified complex at 5 years	Segmental lesion during treatment following measles	Uneventful
K.S.	11	Primary complex right upper lobe; incipient calcification right hilum	Progressive calcification	Calcified complex right upper lobe	"	—	Tuberculous shoulder (See Case 2)
B.F.	8	Primary complex right upper lobe	Considerable regression	Incipient calcification right upper lobe	Calcified complex right upper lobe 2 years onwards	Miliary tuberculosis at 6 months	See Case 5
S.G.	18	Calcifying complexes both upper lobes and hilum	Calcification progressing	Dense bilateral calcifications	Calcification persisting, but decreasing in size at 5 years	Cervical lymph node calcification	Uneventful

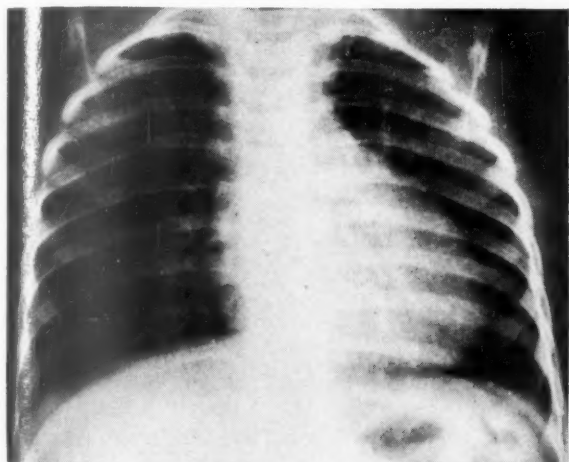


FIG. 13.—J.A. (Table 8): Ill-defined shadows in left lung and primary complex in left lower lobe with incipient calcification on admission.

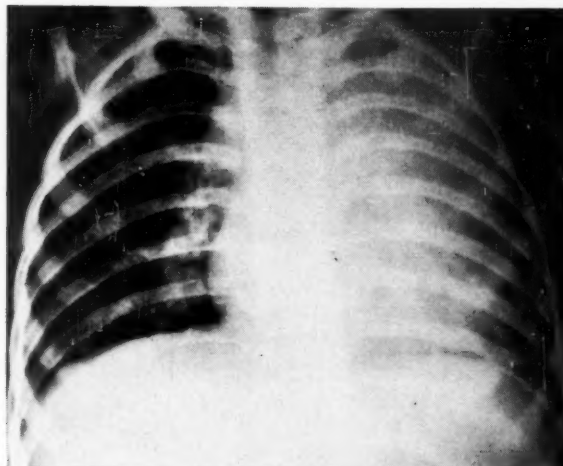


FIG. 14.—J.A.: Three months later: extension of opacity which occupies the whole of the left upper lobe.

tion occurred in B.F. who developed miliary tuberculosis six months after admission.

Dramatic and eventually complete or almost complete clearing of initially extensive lesions occurred in two infants (M.M. and S.R.) (Figs. 15 and 16). In the remaining children the course

of events was one of slow resolution followed by calcification. Five years after admission one of the nine has a clear chest radiograph, one has minimal calcification of the hilar lymph nodes on one side, four have single calcified complexes and three have extensive multiple bilateral calcifications.

TABLE 9

RADIOLOGICAL PROGRESS IN SIX CONTROL INFANTS WITH LARGE OR MULTIPLE PRIMARY COMPLEXES ON ADMISSION

Name	Age O/A (mths)	Radiological Features					Clinical Course
		On Admission	At Three Months	At One Year	Later	Special Features	
S.S.	4	Large mottled shadow right mid-zone and right hilum (Fig. 7)	Worse; left hilum also enlarged; diffuse mottling both sides (Fig. 8)	Large calcifying focus right upper lobe; calcified mass in right hilum; calcified left hilar glands	Dense calcified masses both upper lobes, right lower lobes, both hila and in mesenteric lymph nodes 2-5 years (Fig. 9)	Multiple intra-thoracic and abdominal primary complexes	Repeated stridor (See Case 7)
K.R.	7	Large soft shadows right middle and upper lobes and right hilum	Considerable regression of all shadows	Large calcified mass right middle and upper lobe, and right hilum	No change up to 5 years	Double primary complex	Uneventful
J.C.	23	Opacity left upper lobe and large left hilar nodes	Much better	Hard opacity of left hilum	Returned and remained normal 2-5 years	—	Uneventful
S.B.*	10	Extensive recent complex right upper lobe and right hilum (Fig. 10)	Worse;* ?miliary spread	Much worse;* right upper lobe completely opaque with early calcification (Fig. 11)	Gradual regression of soft shadows, leaving a large calcified complex in right upper lobe at 5 years (Fig. 12)	Deterioration and lobar lesion during treatment	T.B.M. (See Case 8)
S.C.	13	Very extensive fluffy shadows right upper lobe and right hilum	Almost clear	Opacity whole of right middle lobe and large hilar glands again	Regression of pulmonary shadows leaving minimal right hilar calcification only; gross abdominal calcification by 2 years	Double intra-thoracic and abdominal primary foci, lobar collapse at 1 year	Uneventful
L. McB.	13	Fresh large primary complex right upper lobe and right hilum	Slight regression	Incipient calcification in regressed complex	Well calcified small complex right upper lobe 2-5 years	—	Uneventful

\* Treated with streptomycin and P.A.S. from second month onwards.

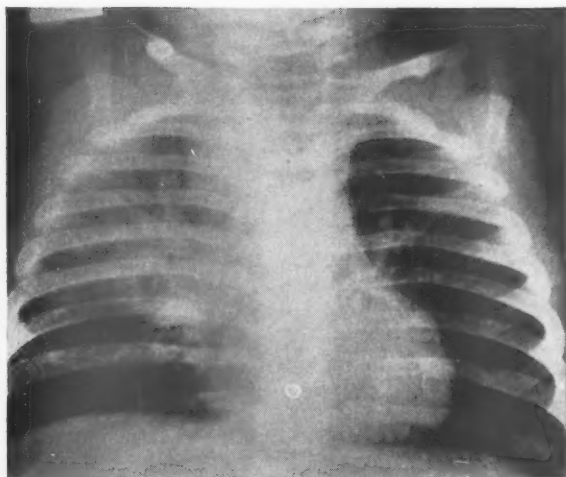


FIG. 15.—S.R. (Table 8): Massive opacity in the right upper and middle lobes with grossly enlarged hilar lymph nodes.

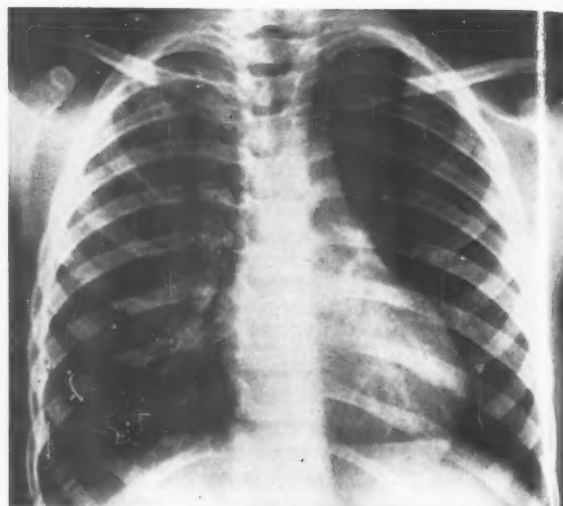


FIG. 16.—S.R.: Normal radiograph four years later: no calcifications.

**Controls:** Two of the six controls (Table 9) showed significant deterioration during the first three months of observation (S.S. and S.B.). The possibility of miliary tuberculosis was considered in both, but remained unconfirmed. One of these infants developed tuberculous meningitis (S.B., Case 8) and although his meningitis responded rapidly to treatment with streptomycin and P.A.S. his lung lesions showed progressive deterioration (Figs. 10-12). Eventually complete healing took place. The other infant recovered without specific treatment, but the extent of his intrathoracic and abdominal calcifications made it clear that he had had disseminated tuberculous lesions (Figs. 7-9). An infant who was 13 months old on admission (S.C.) developed a temporary collapse of his right middle lobe at one year. His clinical course was uneventful. On his final radiograph only a minimal hilar calcification was demonstrable. The latest radiographs in this group of six show that one (J.C.) has a clear chest x-ray, one has minimal calcification of his hilar lymph nodes, one has a small and another a large, single calcified complex and two have large multiple calcified pulmonary complexes. Two children have calcified abdominal glands in addition to their intrathoracic lesions.

(b) 13 INFANTS WITH LOBAR OR SEGMENTAL LESIONS

**Treated Cases:** Three of the seven treated infants (Table 10) showed significant extension of their disease during the three months of treatment. In one of these a segmental collapse became lobar collapse (G.E.), in the second the lesions in the right

middle lobe became more extensive (D.H.), and in the third an already pronounced lobar obstructive emphysema became of extreme degree (J.B.) (Figs. 17 and 18). All the other four infants showed considerable improvement by the time treatment was concluded. In one of these (J.G.) remarkable fluctuations occurred during treatment, large opacities completely disappearing in a matter of days, only to reappear and disappear again in rapid succession (Figs. 19-22).

One year after admission the radiographs were better in all children than at any time earlier. The latest radiographs five years after admission were normal in three children; three had a well calcified single pulmonary complex and one had bilateral calcified complexes. Calcification of the cervical lymph nodes persisted in one child whose pulmonary complex first calcified and later became absorbed (C.M.).

**Controls:** One of the six controls (Case 6, E.R.) (Table 11) developed a haematogenous soft tissue abscess soon after admission and had to be treated with isoniazid and streptomycin. There was only little and slow radiological improvement during the six months of treatment and at the end of five years he still had a segmental collapse in his left upper lobe. This is the only persistent segmental lesion in the entire series of 59 (Figs. 4-6). He also has calcified abdominal lymph nodes.

The remaining five infants in this group required no specific treatment. None deteriorated during the first three months, or at any time later, with the possible exception of B.S. This infant's original lesion showed consistent improvement, but he

TABLE 10

RADIOLOGICAL PROGRESS IN SEVEN TREATED INFANTS WHO PRESENTED WITH LOBAR OR SEGMENTAL LESIONS OR OBSTRUCTIVE EMPHYSEMA ON ADMISSION

Name	Age O/A (mths)	Radiological Features					Clinical Course
		On Admission	At Three Months	At One Year	Later	Special Features	
G.	20	Segmental collapse right middle lobe; glandular mass right hilum	Collapse of whole right middle lobe; glandular mass in right hilum increased; slight right pleural effusion	Much better; faint opacity in region of right middle lobe	Well calcified single complex in right costophrenic angle and right hilum from 2-5 years	Deterioration during treatment; good end result	(See Case 3)
J.C.	6	Complete consolidation of left upper lobe, confluent with left hilar shadow (Fig. 19)	Very slight shadow in left mid-zone	Few calcified specks in the left lingula	Calcifications absorbed; normal radiograph at 4 and 5 years	Remarkable fluctuations during first 3 months (Figs. 19-22)	Uneventful
D.H.	16	Consolidation of right middle lobe; massive glands right hilum; enlarged left hilum	Worse; fresh shadow in right upper lobe and patchy shadowing left upper lobe in addition to previous shadows	Much better; both hila calcifying; small focus right middle and left upper lobes	Well-developed double calcified primary complex right middle and left upper lobes	Deterioration during treatment; good end result; double primary complex	Uneventful
S.C.	9	Consolidation left upper lobe and enlarged mediastinal glands	Considerable regression	Calcified speck left upper lobe, otherwise normal	Calcification absorbed by 3 years, leaving normal radiograph	—	Uneventful
C.M.	9	Large opacity occupying left lingula and enlarged glands left hilum with early calcification	Regression of pulmonary shadows; extensive calcification left hilar and mediastinal lymph nodes	Densely calcified complex left lingula and hilum	Calcification of cervical lymph nodes; pulmonary calcifications absorbed by 5 years	Temporary increase of left perihilar shadows at 15 months; double primary complex	Uneventful
M.N.	22	Obstructive emphysema of entire left lung; big glands left hilum (Fig. 1)	Much better; only considerably enlarged left hilar lymph nodes	Further decrease in left hilar shadow	Calcified complex left upper lobe developing between 2 and 5 years	Rapid improvement ?due to bronchoscopy	(See Case 1)
J.B.	12	Lobar opacity left upper lobe; obstructive emphysema left lower lobe; mass of left hilar glands (Fig. 17)	Worse; gross increase in obstructive emphysema with deviation of mediastinum to right (Fig. 18)	Much improved; minimal emphysema on left	Well calcified primary complex left costophrenic angle and left hilum at 2-5 years	Temporary worsening during treatment; good end result	Uneventful

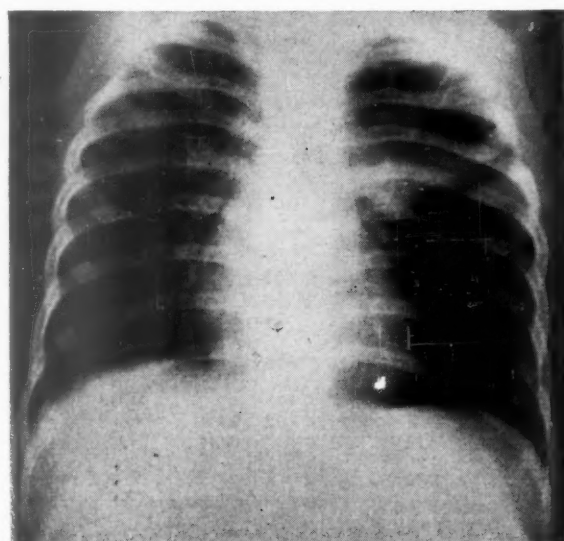


FIG. 17.—J.B. (Table 10): Lobar opacity of left upper lobe and obstructive emphysema of the left lower lobe due to gross hilar lymphadenopathy.



FIG. 18.—Gross increase in degree of obstructive emphysema three months later.

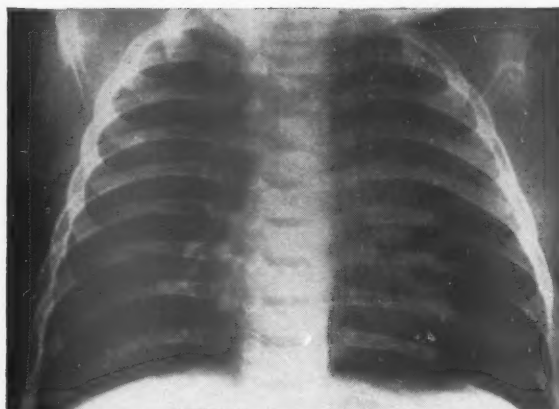


FIG. 19.

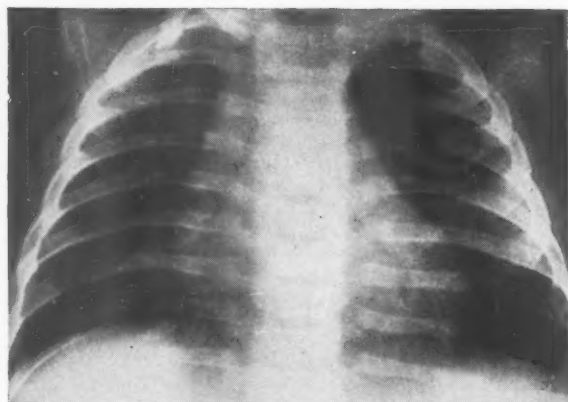


FIG. 20.

FIGS. 19-22.—J.G. (Table 10): Rapidly fluctuating lesions in the left upper lobe and left lingula during the first three months after admission.

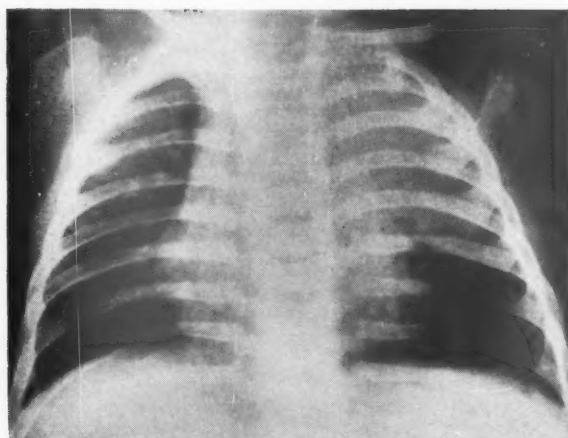


FIG. 21.

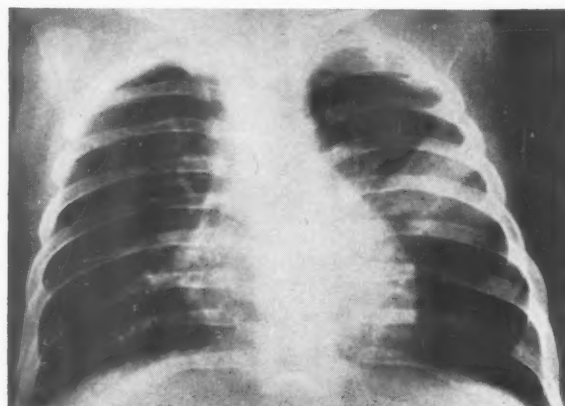


FIG. 22.

developed a lobar consolidation in his other lung on two widely separated occasions. On each occasion this lesion resolved quickly and there was no evidence that it was tuberculous. In three of the five children substantial improvement occurred by three months and in all five by one year. The last radiograph, five years after admission, was normal in two children. Small calcified complexes persisted in the other three.

#### (c) THREE INFANTS WITH PULMONARY TUBERCULOMATA

Finally, there were three infants who had a solitary, large round lesion without comparable degree of enlargement of the hilar lymph nodes (Table 12). The rate of shrinking of the lesion, the degree and type of calcification and the final outcome were similar in the one treated infant and in the two controls. None showed improvement by three months, but a reticular type of calci-

fication developed and the tuberculoma started to contract by one year. This process continued and now all three have a dense calcified mass which is much smaller than the original lesions. Small adjacent calcified primary complexes became demonstrable in all three (Figs. 23-31).

(4) *Summary of Radiological Changes.* There were nine infants with no demonstrable pulmonary lesions at any time. Seven of them had primary abdominal complexes. Among the remaining 51 children there were 20 who had either no demonstrable lesion on admission or had hilar glandular enlargement only. No subsequent deterioration was seen in any of these. They all developed pulmonary calcified complexes, irrespective of whether they were treated with isoniazid or not.

All the important changes occurred among the 31 who already had gross lesions on admission. The most serious complications seen were miliary

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TABLE 11

RADIOLOGICAL PROGRESS IN SIX CONTROL INFANTS WHO PRESENTED WITH LOBAR OR SEGMENTAL LESIONS ON ADMISSION

Name	Age O/A (mths)	Radiological Features					Clinical Course
		On Admission	At Three Months	At One Year	Later	Special Features	
E.R.*	11	Extensive opacity with central calcification occupying the whole left upper lobe; calcifying glands in neck (Fig. 4)	Decreasing mass left upper lobe with extensive calcification in it; splenic and mesenteric calcifications ++	Left upper lobe collapse; additional calcified focus in left lower lobe, otherwise same (Fig. 5)	Segmental collapse of left upper lobe persisted at 5 yrs; extensive calcifications in left upper, left lower lobes, left hilum (Fig. 6); cervical and mesenteric nodes* in spleen	Deterioration during isoniazid treatment, persistent collapse; multiple ? primary foci; splenic calcifications	(See Case 6)
L.W.	6	Massive opacity occupying the pectoral segment of right upper lobe, glands, right hilum	Substantial general improvement	Small calcifying focus, right upper lobe; glandular mass denser	Well calcified double but small primary complex right upper lobe from 2-5 years	Rapid improvement	Uneventful
J.D.	18	Opacity occupying the whole of the left lingula	Substantial improvement	Small calcifying focus left lingula and left hilar nodes	Very small calcified complex left lingula persisting at 5 years	Rapid improvement	Uneventful
D.G.	13	Consolidation of right middle lobe	No improvement	Much better; only right hilar enlargement	Returned to normal at 2 years and remained so at 5 years; no calcification	Complete clearing of big lesion	Uneventful
L.Z.	4	Segmental opacity left upper lobe; enlarged glands left hilum	No improvement	Opacity smaller and denser; glands not demonstrable	Minimal calcified complex left upper lobe at 3 years, and normal at 5 years	—	Uneventful
B.S.	3	Enlarged gland left hilum; obstructive emphysema left lower lobe	Much improved—emphysema less obvious	Large calcified gland left hilum	Small calcified complex left lower lobe at 2-5 years	Intercurrent symptomless consolidation of whole of right middle lobe at 5 and 15 months after admission with complete clearing within 1 month each time	Uneventful

\* Treated with isoniazid and streptomycin for 6 months, starting one week after admission.

TABLE 12

RADIOLOGICAL PROGRESS IN THREE INFANTS WHO PRESENTED WITH PULMONARY TUBERCULOMA ON ADMISSION

Name	Age O/A (mths)	Radiological Features					Clinical Course
		On Admission	At Three Months	At One Year	Later	Special Features	
(a) Treated T.W.	21	Very large uniformly dense mass in region of right middle lobe; no apparent glandular enlargement (Fig. 23)	Same	Shadow smaller; dense reticular calcification throughout its substance (Fig. 24)	Progressive shrinking of lesion with increasing dense calcification; very dense contracted mass at 4-5 years; minimal hilar gland calcification 3-5 years (Figs. 25-26)	—	Uneventful
(b) Controls N.K.	17	Dense round opacity occupying left lingula; no apparent glandular enlargement (Fig. 27)	Same	Reticular calcification throughout substance of lesion; small calcifying gland in left hilum (Fig. 28)	Progressive shrinking of lesion with increasingly dense calcification; small calcified gland left hilum 3-5 years (Figs. 29-31)	—	Uneventful
P.B.	13	Large round shadow in right middle lobe without apparent glandular enlargement	Same	Reticular calcification developing in shrinking tuberculoma; additional small calcifying complex right lower lobe and hilum	Progressive shrinking and increasing calcifications at 5 years	—	Uneventful

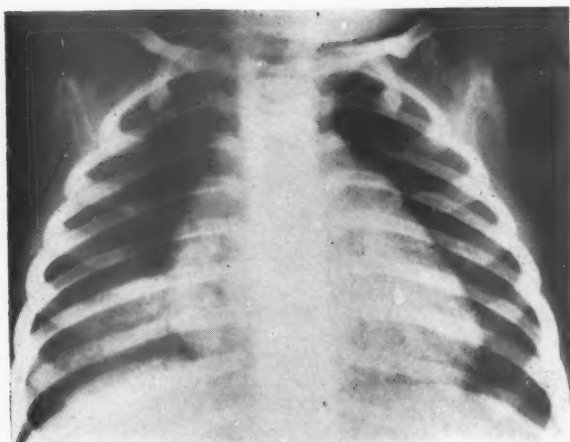


FIG. 23.

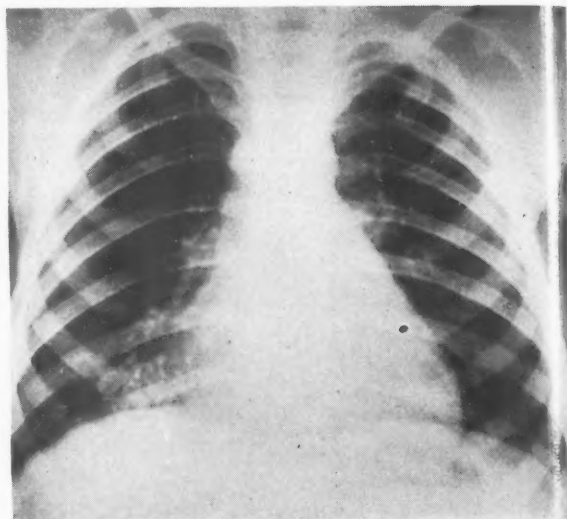


FIG. 24.

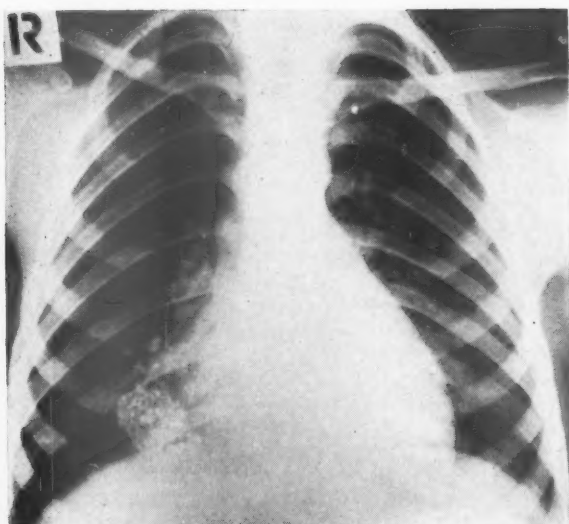


FIG. 25.



FIG. 26.

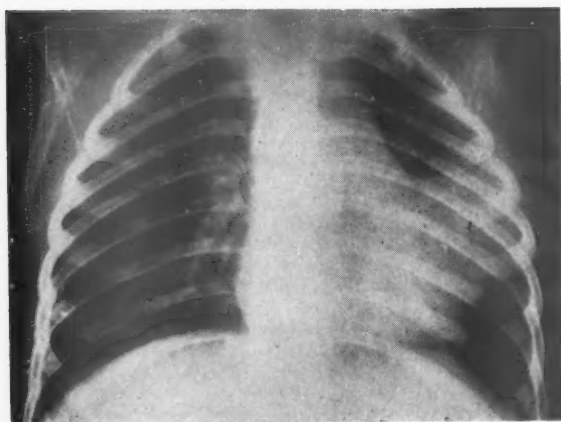


FIG. 27.

FIG. 23.—T.W. (Table 12): Fresh tuberculoma in right middle lobe, on admission.

FIG. 24.—T.W.: Reticular calcification taking place one year later.

FIGS. 25 and 26.—T.W.: Dense residual calcified mass five years later.

FIG. 27.—N.K. (Table 12): Fresh tuberculoma in left lingula on admission.

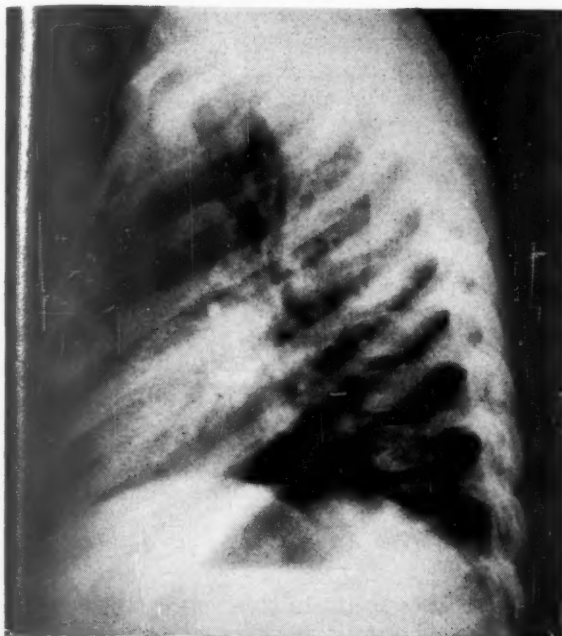


FIG. 28.—N.K.: Reticular calcification one year later.



FIG. 30.

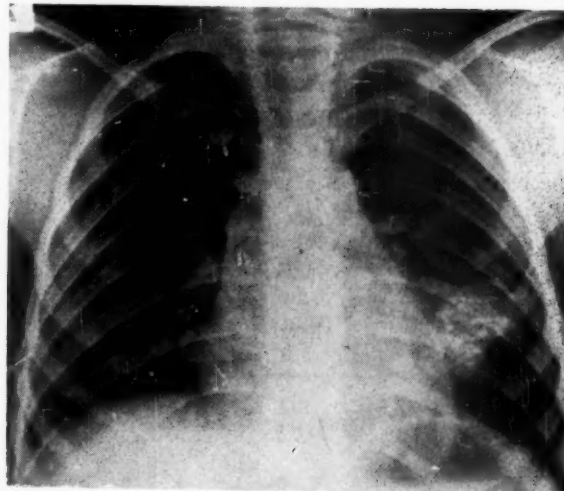


FIG. 29.

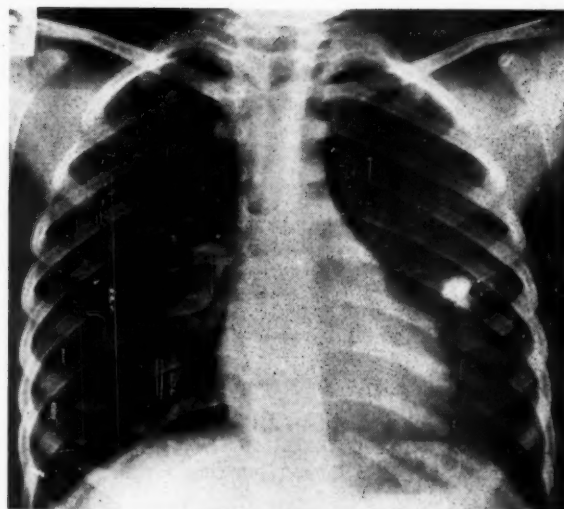


FIG. 31.

FIGS. 29-31.—N.K.: Progressively dense calcification and regression.

tuberculosis in a treated infant, three months after the conclusion of treatment; and persistent segmental collapse in a control who had to be given a prolonged course of treatment starting soon after his admission. Considerable but temporary deterioration occurred during the first year after admission in six treated infants and in three controls.

The latest radiographs (Table 13) show that of the 3) treated children 10 have no detectable lung lesion, 2) have intrathoracic and four extrapulmonary calcification. These figures compare with seven out

of 29 controls with negative radiographs of the chest, and 22 with calcified intrathoracic lesions. Seven children have calcified abdominal lymph nodes, including three who have intrathoracic as well as abdominal calcifications. This number includes two children who had to receive chemotherapy. These two have the most extensive residual lesions.

#### Discussion

This investigation failed to indicate that isoniazid associated with P.A.S. conferred any demonstrable

TABLE 13

## INCIDENCE OF CALCIFIED LESIONS ON THE FINAL RADIOGRAPHS

	Treated				Controls			
	Number	Lung Calcification	Abdomen or Neck Calcifications	No Lesion	Number	Lung Calcification	Abdomen or Neck Calcifications	No Lesion
Initially negative .. ..	9	3	3	3	8	4	4	—
Hilar glandular enlargement only .. ..	4	4	—	—	7	7	—	—
Single or multiple primary lesions .. ..	9	8	—	1	6	5*	2*	1
Segmental or lobar lesions ..	7	4*	1*	3	6	4†	1†	2
Tuberculomas .. ..	1	1	—	—	2	2	—	—
Total .. ..	30	20*	4*	7	29	22*†	7*†	3

\* Multiple calcified foci.

† One child treated with INH and SM almost from beginning.

benefit on infants suffering from uncomplicated primary tuberculosis. The absence of significant differences between the two groups, however, was not so much due to the failure of treatment, as to the fact that primary tuberculosis even in these very young infants is usually a benign condition in this country. It is possible that if the duration of isoniazid treatment had been longer, the miliary tuberculosis which occurred after the conclusion of treatment might have been avoided. In the same way the single case of tuberculous meningitis might not have occurred if the infant had been on prophylactic isoniazid. If it had been possible to study a much larger group of children more conclusive differences might have emerged. The number of cases of primary tuberculosis in our community, however, was diminishing so rapidly that the continuation of this investigation would hardly have added enough new children to reach more definite conclusions. Nevertheless, the data from this investigation are sufficient to show that the course of the primary infection and the evolution of the primary lesion itself are not favourably influenced by antibiotic treatment.

It is still important to know whether isoniazid, used prophylactically in infected children, is likely to prevent local extension of the disease, haematogenous spread or tuberculous meningitis. Some answers are available to this problem from a similar, but large-scale co-operative investigation performed in the United States and initiated by Dr. E. M. Lincoln. A preliminary communication (Ferebee, Mount and Anastasiades, 1957) has been published. Twenty-one clinics enrolled 2,750 children between January 1955 and June 1957. They were tuberculin positive and those over 3 years of age also had to have radiological evidence of tuberculosis, though in practice this was not always adhered to. Children

were allocated by the random sampling method into two groups. In one group treatment was given by isoniazid (4-6 mg./kg. body weight) daily for 12 months. The other group received identical placebo tablets and the physicians treating the children were not aware to which group their patients belonged.

The initial analysis of the results showed that during the first year of observation six cases of tuberculous meningitis occurred among the controls and only one among the treated. There were, however, two cases of miliary tuberculosis in the treated and one among the controls. Five controls and one treated child developed skeletal tuberculosis. Altogether 26 controls and five treated children had some extrapulmonary complications. These differences are statistically significant, but it must be remembered that to prevent these 21 clinical cases, many of which were trivial, nearly 1,400 children had to be treated for a whole year with a drug which is not free of toxic side-effects. Further, we do not know what influence, if any, this treatment will have on the late development of adult type of tuberculosis, nor do we know the outcome of further antibiotic treatment in those who have already had one year's treatment and may harbour resistant organisms. The incidence of meningitis and miliary tuberculosis in the controls was only 0.5%, even though little over one-fifth (296 out of 1,356) were children of white stock. The report does not subdivide the results according to race, though this may be of importance.

There was no significant difference between the two groups with regard to the development of adverse pulmonary changes developing during the first year, though only 21 of those treated with isoniazid developed these as compared with 34 controls. An analysis of the results in the controls

showed that children under 1 year of age were at the greatest risk of developing meningitis. This risk was 33 per 1,000 for those with normal roentgenograms, 100 per 1,000 for those with hilar or paratracheal involvement, and 182 per 1,000 for those with parenchymal involvement. It is not stated how many infants were of this age group, nor how many were of European stock, so that too much should not be read into these figures. The risk of developing meningitis in children over 1 year of age was trivial.

There is now a very large volume of literature on the treatment of primary tuberculosis. The only other major attempt at a controlled therapeutic trial was organized by the Institut National d'Hygiène in Paris and other French cities (Lotte, Noufflard, Debré and Brissaud, 1960). Unfortunately, in this trial, individual physicians were given the liberty to treat or not treat children, according to their clinical judgment, so there were admittedly no real controls. Altogether 5,526 children were enrolled, many retrospectively. In this trial chemotherapy consisted of isoniazid (20 mg./kg. per day) plus P.A.S. (300 mg./kg. per day) for a minimum of six months. The incidence of extrapulmonary complications was commonest in the controls who were under 5 years of age (0.7% versus 12.6%), but pulmonary complications were commoner in the treated children. Out of 153 treated cases, 21 developed atelectasis (13.8%). No systematic or serial gastric washings were performed, but strains of tubercle bacilli were cultured from 14 patients after three months of treatment. Two strains were highly resistant and one slightly resistant to isoniazid.

Lincoln, Harris, Bovornkitti and Carretero (1958) studied 156 children (111 under 2 years of age) with primary tuberculosis with serial bronchoscopy. They found that endoscopic evidence of bronchial tuberculosis was commonest in children under 4 years. Three-quarters of their patients had had chemotherapy, but endobronchial involvement persisted for one to over three years in spite of it, and 50 of the 156 developed gross abnormalities of the bronchial tree as shown on bronchogram. They conclude: 'There is no evidence that antimicrobial therapy shortens the course of tuberculous endobronchitis due to encroachment of caseous nodes in the bronchi. Specific therapy does not diminish the incidence of sequelae in the bronchi or the parenchyma. Nevertheless, there is justification for treating children with tuberculous endobronchitis in the hope of diminishing the dangers of bronchogenic spread.' Lorriman and Bentley (1959) had similar experience and came to similar conclusions,

as did Frostad (1959), who noted perforation of the bronchial wall by caseous lymph nodes in 23 children two to 14 months after the beginning of chemotherapy.

Lambert (1959), in reviewing the evidence in favour of prophylactic treatment with isoniazid in symptomless children, concludes that it is undesirable because of our ignorance of its effects on the patients' subsequent immunity and their liability to harbour drug-resistant bacilli. Tuberculin reversion took place in four infants aged 7 to 24 months after six months of isoniazid treatment (Robinson, Meyer and Middlebrook, 1955).

### Conclusions

In conclusion, it seems evident that at the present the immediate prognosis of primary tuberculosis in even very young English children is generally favourable and specific treatment of complications is so successful that it is not essential or perhaps even desirable to treat symptomless tuberculous infants with specific drugs, or admit them to hospital as long as they are under adequate outpatient supervision and the parents and their doctors are conversant with the earliest symptoms which might indicate extrapulmonary spread of the tuberculosis which will demand treatment. A watchful expectant policy can be justified, knowing the actual treatment of the complications is little different from the so-called prophylactic treatment and that the outcome of therapy is excellent, if it is applied early. Adopting such a policy, one will only need to treat perhaps one in 10 infants and a much smaller proportion of older children. These conclusions do not necessarily apply under different racial, social or economic conditions in different parts of the world.

### Summary

A strictly controlled therapeutic trial in the treatment of primary tuberculosis in infancy is reported. Fifty-nine infants were enrolled and observed for five years. Thirty were treated with isoniazid and P.A.S. and the others served as controls.

A detailed analysis of their progress failed to disclose that the antibiotic treatment conferred any benefit on the treated infants.

The indications for prophylactic chemotherapy are discussed.

I am happy to acknowledge the help received from physicians of the Sheffield Chest Clinic who referred most of the cases; Dr. Llywelyn Roberts, Medical Officer of Health and his staff of Health Visitors who

arranged the children's attendance and kept an eye on potential defaulters; Dr. T. Lodge and his staff for the many radiographs, and Professor R. S. Illingworth for his encouragement of this work and for his critical comments.

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# BRITISH PAEDIATRIC ASSOCIATION

## Proceedings of the Thirty-second Annual Meeting

The Annual Meeting of the British Paediatric Association was held in Cambridge from June 27 to 30, 1961, and was held jointly with the Canadian Paediatric Society.

The following members of the Association were present:

A. W. Abramson, A. G. V. Aldridge, F. M. B. Allen, E. C. Allibone, I. M. Anderson, H. Angelman, J. Apley, G. C. Arneil, M. W. Arthurton, Cecile Asher, M. D. Baber, A. D. Barlow, T. E. D. Beavan, J. A. Black, A. C. Blandy, M. Bodian, R. E. Bonham Carter, J. P. Bound, Frances Braid, J. V. Braithwaite, T. A. Brand, F. S. W. Brimblecombe, D. J. Browne, R. J. K. Brown, M. F. G. Buchanan, J. Burkinshaw, N. R. Butler, E. A. J. Byrne, W. A. B. Campbell, W. H. P. Cant, I. A. B. Cathie, H. M. T. Coles, W. R. F. Collis, T. Colver, C. E. Cooper, B. D. Corner, D. G. Cottom, S. D. M. Court, John Craig, J. O. Craig, Mildred Creak, R. D. G. Creery, K. W. Cross, A. A. Cunningham, S. B. Dimson, M. E. Disney, E. F. Dott, D. M. Douglas, E. E. Doyle, A. C. Doyne-Bell, S. Dundon, Margaret Egan, H. L. Ellis, R. W. B. Ellis, J. L. Emery, P. R. Evans, C. G. Fagg, G. Fanconi, H. G. Farquhar, G. V. Feldman, C. Elaine Field, H. V. L. Finlay, H. J. W. Fisher, O. D. Fisher, R. M. Forrester, Isabella Forshall, A. White Franklin, Muriel J. L. Frazer, A. A. H. Gailey, W. F. Gaisford, W. H. Galloway, D. M. T. Gairdner, B. Gans, J. M. Garvie, H. M. Giles, R. R. Gordon, I. H. Gosset, S. Graham, J. L. Greaves, Sylvia K. Guthrie, C. F. Harris, E. W. Hart, C. C. Harvey, J. D. Hay, J. L. Henderson, W. Henderson, G. Hesling, E. Hinden, K. S. Holt, A. Holzel, D. V. Hubble, F. P. Hudson, J. H. Hutchison, R. S. Illingworth, T. T. S. Ingram, R. J. Isaac, A. D. M. Jackson, J. Jacobs, R. T. Jenkins, H. Jolly, H. Everley Jones, S. Keidan, J. J. Kempton, A. C. Kendall, C. W. Kesson, G. Komrower, B. M. Laurance, D. N. Lawson, R. C. Lightwood, J. Lorber, J. Luder, P. MacArthur, J. C. Macaulay, R. A. McCance, D. MacCarthy, M. McGregor, Muriel McLean, B. McNicholl, T. Mann, W. J. Matheson, R. M. Mayon-White, F. J. W. Miller, R. G. Mitchell, A. A. Moncrieff, Zina Moncrieff, David Morris, J. H. Moseley, P. D. Moss, F. W. Nash, A. V. Neale, G. A. Neligan, C. E. Newman, G. H. News, D. N. Nicholson, A. P. Norman, J. N. O'Reilly, A. P. M. Page, D. Paterson, C. G. Parsons, W. W. Payne, J. D. Pickup, C. P. Pinckney, P. Polani, B. W. Powell, L. J. Prosser, R. J. Pugh, J. F. P. Quinton, J. P. R. Rees, I. D. Riley, A. P. Roberts, E. G. G. Roberts, J. A. Fraser Roberts, T. S. Rodgers, K. B. Rogers, J. Rubie, A. Russell,

J. Sakula, T. R. Savage, B. Schlesinger, L. G. Scott, W. H. P. Sheldon, Ursula Shelley, Victoria Smallpeice, R. E. Smith, J. M. Stansfield, T. Stapleton, D. G. H. Stone, P. N. Swift, K. H. Tallerman, M. L. Thomson, John Thomson, D. C. Thursby-Pelham, J. J. Tillie, J. P. M. Tizard, R. McL. Todd, W. M. L. Turner, D. G. Vulliamy, O. C. Ward, C. B. M. Warren, A. G. Watkins, B. W. Webb, S. D. V. Weller, R. White-Jones, I. G. Wickes, R. Wigglesworth, H. P. Williams, D. A. J. Williamson, Mary J. Wilmers, B. D. R. Wilson, D. W. Winnicott, O. H. Wolff, B. Wolman, B. S. B. Wood, B. Woodhead, T. Wright, R. J. Young, Winifred Young, S. Yudkin, R. B. Zachary.

The following members of the Canadian Paediatric Society were present:

Pierre H. Beaudry, Stanley C. Best (President), Edna L. Birchard, J. Nixon Briggs, H. R. Brodie, David Burnford, E. A. M. Cairns, James Calder, William Cochrane, Anne R. Cole, N. Barrie Coward, J. H. Ebbs, J. M. Elder, Urban J. Gareau, Alton Goldbloom, R. R. Goldbloom, Alice M. Goodfellow, R. H. Hill, James Hingston, G. H. Holman, Wanda J. Jegier, H. M. Keith, H. Krivel, C. S. Livingstone, P. C. MacGillivray, J. Kenneth Martin, Agnes K. Moffat, Granville Nickerson, A. J. de Pape, Clare Randall, J. C. Rathbun, M. H. Roberts, C. R. Sriver, J. Boyd Sriver, Walter M. Sriver, C. E. Snelling, Paul R. Swyer, J. Mavis Teasdale, W. W. Tidmarsh (Secretary), J. A. P. Turner, G. H. Valentine, Patrick Wei, C. Collins-Williams, R. A. Wilson, W. J. Wilson, M. D. Young.

The following were present as guests of the Association:

Professor J. S. Mitchell (Regius Professor of Physics in the University of Cambridge), J. Woodcock, Esq., G. J. Piller, Esq., Dr. L. A. Strang and Dr. J. Davis.

The following were present as guests of members of the Association:

J. D. Allan, Margaret Belton, A. B. Bergman, R. T. Binns, B. D. Bower, Gillian Brunton, A. H. Cameron, D. M. Cathro, K. Christie, Barbara Clayton, P. J. N. Cox, G. S. Dawes, Constance Forsyth, W. M. Fyfe, H. R. Gamsu, O. P. Gray, Margaret Griffiths, J. A. Hill, June R. Hill, C. G. Hinton, J. Insley, D. Jackson, M. C. Joseph, I. Kessel, L. Lawn, C. Lowe, Alison McDonald, N. R. Mackay, D. MacMillan, Marion Miles, J. Mishra, J. N. Montgomery, D. C. Morley, T. E. Oppé, F. J. C. Perera, J. W. Platt, C. A. Reindorf, J. Rees Roberts, Janet D.

Roscoe, R. C. Roxburgh, Mary D. Sheridan, S. de Silva, K. Simpson, E. A. Smedal, R. W. Smithells, L. H. Stevens, W. B. Steitz, M. A. Warley, W. B. Weild, A. W. Wilkinson, Wong Hock Boon.

The Annual General Meeting was held on Wednesday, June 28, with the President, Professor A. V. Neale, in the Chair.

The Minutes of the last meeting, which had been published in the *Archives of Disease in Childhood*, were received and approved.

**ELECTION OF OFFICERS.** The following were elected:

PRESIDENT: Professor A. A. Moncrieff

PRESIDENT-ELECT: Dr. C. F. Harris

HONORARY TREASURER: Professor A. G. Watkins

HONORARY SECRETARY: Dr. E. W. Hart

**EXECUTIVE COMMITTEE, 1961-1964:**

Dr. F. S. W. Brimblecombe, Dr. R. M. Mayon-White, Dr. G. A. Neligan, Dr. R. A. Shanks.

**ELECTION OF MEMBERS.** The following were elected:

#### HONORARY MEMBERS

Dr. J. V. Braithwaite, Professor A. V. Neale, Professor H. J. Seddon.

#### CORRESPONDING MEMBERS

Livmedikus Erik Böttiger and Professor C. Salazar de Sousa.

#### ORDINARY MEMBERS

J. D. Allan (Manchester), R. F. Barbour (Bristol), B. D. Bower (Birmingham), Mary Capes (Southampton), P. J. N. Cox (London), G. S. Dawes (Oxford), W. I. Forsythe (Belfast), W. M. Fyfe (Glasgow), O. P. Gray (Cardiff), A. J. Keay (Edinburgh), J. N. Montgomery (Plymouth), T. E. Oppé (London), J. W. Platt (Cumberland), J. R. Roberts (Liverpool), Janet D. Roscoe (Cambridge), R. C. Roxburgh (King's Lynn), Olive Scott (Liverpool), Mary D. Sheridan (London), K. Simpson (Leicester), R. W. Smithells (Liverpool), F. H. Stone (Glasgow), Dorothy M. Taylor (London).

The Treasurer's report and statement of accounts for the year 1960-61 were received and approved, and the auditors were reappointed for the next year. The report of the council was received and approved and is printed below:

#### Report of the Council, 1960-61

**OBITUARY.** The Association has suffered the loss of two Honorary members, Professor James Smellie, an original member and former President, and Sir Thomas Fairbank; and also the loss of one Corresponding member, Professor Alan Brown, and one Ordinary member, Dr. D. W. Beynon.

#### COUNCIL MEMBERS

The membership of the Council during 1960-61 has been: Professor A. V. Neale, Dr. J. Apley, Dr. W. A. B. Campbell, Dr. P. R. Evans, Dr. A. W. Franklin,

Dr. E. W. Hart, Dr. W. Henderson, Professor D. V. Hubble, Dr. G. Komrower, Dr. R. C. Lightwood, Dr. P. MacArthur, Professor A. A. Moncrieff, Dr. L. C. Scott, Dr. Victoria Smallpeice, Dr. J. P. M. Tizard, Professor A. G. Watkins, Mr. R. B. Zachary.

The following are invited to attend as observers: Dr. C. Asher (Ministry of Education); Dr. J. C. R. Buchanan (Colonial Office); Sir Wilfrid Sheldon (Adviser in Child Health to the Ministry of Health); Dr. Dorothy Taylor (Ministry of Health).

The Council met in November 1960 and in February and April 1961, and met again on June 27, 1961. In addition to receiving reports from sub-committees (see below) the following matters were considered:

The Council noted with great pleasure the distinctions conferred on Sir Denis Browne, K.C.V.O.; the award of the Conway Evans Prize of the Royal College of Physicians to Professor R. A. McCance; and the election of Dr. R. E. Steen as President of the College of Physicians of Ireland.

1. **JAMES SPENCE MEDAL.** The Council has pleasure in announcing the award of the James Spence Medal. 1960: Professor A. A. Moncrieff; 1961: Professor R. A. McCance.

The medals will be presented at the Annual General Meeting in Cambridge.

2. **VISIT TO SWEDEN.** Twenty members of the Association visited Sweden in September 1960 as guests of the Swedish Paediatric Society and enjoyed great hospitality. Three members delivered lectures to students and six members gave communications at meetings with the Swedish Paediatric Society.

3. **HEINZ FELLOWSHIPS OF THE BRITISH PAEDIATRIC ASSOCIATION.** The establishment of these Fellowships was reported by the President at the 1960 Annual General Meeting. The Fellowships for 1961 were awarded to Dr. G. H. Holman of Saskatoon, Dr. Wong Hock Boon of Singapore, and Dr. C. Reindorf of Ghana. The Fellows will be present at the Annual Meeting in Cambridge.

4. **HOME CARE SCHEMES.** The report of the sub-committee (J. Apley, F. S. W. Brimblecombe, D. Gairdner, M. MacGregor (Convener) and L. G. Scott) was received and approved. Copies of the memorandum were circulated to all paediatricians. Copies were also sent to the Chief Medical Officers, Ministry of Health, Department of Health for Scotland and Ministry of Health and Local Government, Northern Ireland, and to S.A.M.O.s, Regional Hospital Boards, the Society of Medical Officers of Health, and County Medical Officers.

5. **INTERNATIONAL PAEDIATRIC ASSOCIATION.** After discussions concerning the future organization of the International Paediatric Association, Professor A. G. Watkins attended an *ad hoc* committee meeting in Zurich in April 1961, to present the views of the Association.

6. **NATIONAL BUREAU FOR CO-OPERATION IN CHILD CARE.** The proposed establishment of the Bureau has been discussed by the Council and Dr. A. White Franklin

has attended meetings to represent the views of the Association.

7. MEDICAL SERVICES REVIEW COMMITTEE. The Association were invited to complete a questionnaire and did so, only in so far as matters of paediatric importance were concerned.

8. COMMITTEE ON MEDICAL STAFFING STRUCTURE IN THE HOSPITAL SERVICE. Following the submission of a written memorandum, the Association gave oral evidence to the Committee (E. W. Hart, P. MacArthur, M. MacGregor and A. G. Watkins). The report of the Platt Committee has now been published.

9. THE CARE OF THE YOUNG CHRONIC SICK. An invitation from the Department of Health for Scotland to submit a memorandum on this topic was accepted. A sub-committee (G. C. Arneil, R. W. B. Ellis, J. L. Henderson and P. MacArthur (Convener)) have prepared and submitted a memorandum, which has been approved by the Council.

10. INFECTIOUS DISEASES HOSPITALS SUB-COMMITTEE. A questionnaire was sent to all paediatricians and met with a 95% response. The analysis continues and the problem is being further considered by the sub-committee (P. R. Evans (Convener), F. F. Kane and H. Jolly).

11. HYPERCALCAEMIA SURVEY. The sub-committee has been asked to extend the survey for a further year and to include cases of rickets and scurvy up to the age of 5 years. T. Oppé has replaced T. Stapleton as secretary.

12. CHILD HEALTH SERVICES FOR GREATER LONDON. The Council has noted the suggestions of the Royal Commission for the organization of the local government of Greater London in so far as they concern the Child Health Services. A sub-committee has been formed to consider the matter (the President (*ex officio*), the Secretary (*ex officio*), R. E. Bonham Carter, D. G. Cottom (Convener), M. MacGregor and S. Yudkin).

13. REVIEW OF PAEDIATRIC STAFFING PROBLEMS. The review continues.

#### STANDING COMMITTEES

MENTAL HEALTH (formerly Child Psychology): J. Apley, Mildred Creak, D. V. Hubble, R. Mac Keith, D. MacCarthy, R. M. Mayon-White, C. T. Potter, J. P. M. Tizard.

The Committee has reported to the Council at each meeting. Discussions with the Mental Deficiency section of the Royal Medico-Psychological Association continue. The report of the Committee 'Psychiatric Services for Children' was published in the *British Medical Journal*, September 10, 1960.

NURSING: J. D. Hay, E. W. Hart, R. S. Illingworth, P. MacArthur, W. Sheldon, D. J. Waterston, A. G. Watkins.

The Committee has had discussions with the British Association of Paediatric Nurses concerning the training of paediatric nurses. The two Associations jointly sent a letter to the Headmistresses Association drawing their attention to paediatric nursing as a career and asking them to inform their pupils. The Committee, together with the British Association of Paediatric Nurses, requested an interview with the Education Committee

of the General Nursing Council to discuss the future of paediatric nursing. B.P.A. representatives (E. W. Hart, W. H. P. Sheldon and A. G. Watkins) raised questions on the future of the Children's Register, the continued use of the small Children's Hospitals as training schools, and possible future plans for paediatric nurses' training. Subsequent discussion with the British Association of Paediatric Nurses is hoped for.

TROPICAL PAEDIATRICS: R. W. B. Ellis, R. Lightwood, M. MacGregor, A. A. Moncrieff, A. G. Watkins, Cicely Williams.

No report.

STANDING JOINT COMMITTEE WITH R.C.O.G.: P. R. Evans, J. H. Hutchison, R. Lightwood, F. J. W. Miller, A. A. Moncrieff. The Committee has not met.

JAMES SPENCE MEDAL COMMITTEE: C. G. Parsons, F. J. W. Miller, P. R. Evans, R. W. B. Ellis, the Secretary (*ex officio*). The Committee has submitted a report to the Council and has recommended that medals should be cast for award for 1960 and 1961.

ACCIDENTS IN CHILDHOOD: The Council has formed a Standing Committee as the problem of accidents in childhood has assumed such great importance. J. O. Craig, Isabella Forshall, R. C. Mac Keith, Victoria Smallpeice, S. Yudkin, R. B. Zachary. The Committee has held discussions concerning the desirability of establishing a Poisons Centre for the country as a whole. After conferring with the other committees interested in this problem, a direct approach to the Minister is to be made.

The Committee has obtained representation on the Osmond-Clarke Committee on 'Accident Services and Units' and a memorandum on the special needs of children in such services has been submitted.

#### B.P.A. REPRESENTATIVES:

Joint Tuberculosis Council: Professor W. F. Gaisford.

Leonard Parsons Memorial Committee: Professor S. Graham.

United Kingdom Committee for Poliomyelitis: Dr. E. W. Hart.

National Association for Mental Health: Dr. J. Apley.

Standing Maternity and Midwifery Advisory Committee of Ministry of Health: Dr. J. Forest Smith.

Standing Maternity Hospital Report Committee of R.C.O.G.: Professor A. A. Moncrieff.

Nursery Schools Association Medical Advisory Committee: Dr. L. G. Scott.

National Association for Maternity and Child Welfare: Dr. A. White Franklin.

#### NOTICES

Tenth International Congress of Paediatrics:

The Congress will be held in Lisbon from September 9-15, 1962.

The Registration period will be August 1, 1961 to January 31, 1962.

When further information is available, members will be notified.

Leonard Parsons Memorial Lectures:—

These lectures were given in Birmingham on June 5 and 6, 1961.

Dr. Lawson Wilkins lectured on Adrenal Disorders. I. Cushing's Syndrome and its Puzzles. II. The Adrenogenital Syndrome and its Solution.

#### ANNUAL MEETING

A reception was held on the evening of Tuesday, June 27, in the Old Schools, by courtesy of the Council of the Senate, University of Cambridge.

Scientific sessions were held in the Guildhall on Wednesday, June 28 and Thursday, June 29.

The George Frederic Still Memorial Lecture was delivered by Dr. J. H. Ebbs (Toronto) on 'Moniliasis'.

#### SCIENTIFIC SESSIONS

B. M. LAURANCE (Derby). 'Hypotonia, Obesity, Hypogonadism and Mental Retardation in Childhood.' Six children are described who, shortly after birth, were so hypotonic that several were considered to have 'amyotonia congenita'. Subsequently, 'milestones' have been reached late, and mental ability has only progressed to the educationally sub-normal standard. All have become obese and have a strikingly similar facial appearance. The scrotum is underdeveloped and the gonads impalpable; in one child, no gonads could be found at operation. Investigations suggest that some of these children are pre-diabetic, which confirms Fanconi's report that diabetes occasionally develops in this syndrome. The children are chromatin negative and have normal chromosomes.

C. R. SCRIVER (Montreal), J. H. HUTCHISON (Glasgow) and D. B. COURSON (Lancaster, U.S.A.). 'Vitamin B<sub>6</sub> Deficiency in Human Infant: Biochemical Observations of Amino Acid and Coenzyme Metabolism.' We have studied a 14-month female with seizures and vitamin B<sub>6</sub> deficiency. Pyridoxine supplements corrected clinical and biochemical abnormalities, which reappeared following supplement withdrawal.

Biochemical disturbances were selective, affecting cystathionine, cysteine, tryptophan and, by inference, gamma-aminobutyrate metabolism; transamination in general was unaffected. The expected preference for available coenzyme was therefore demonstrated.

The actual vitamin B<sub>6</sub> requirement of the infant was 3.0 mg. daily, which exceeded both normal requirement and her potentially adequate daily intake (0.8-1.2 mg.). Coenzyme deficiency and elevated vitamin requirements seemed accountable to a deviation of vitamin B<sub>6</sub> metabolism, from actual coenzyme formation, to excessive oxidation ('4-pyridoxic acid shunt').

DUNCAN MACMILLAN (Birmingham), introduced by Professor D. V. Hubble. 'The Growth Hormone Assay and Disorders of Growth.' Read's method for the assay of human growth hormone depends on the inactivation of rabbit anti-growth hormone serum by growth hormone contained in the serum to be tested. Growth hormone-coated sheep erythrocytes are used to

indicate the degree of this reaction as they are agglutinated only in the presence of residual antibody.

This assay has now been applied both in normal children and in children suffering from various disorders of growth—including congenital hypopituitary dwarfism, primordial dwarfism, progeria, hypothyroidism, gigantism and obesity. The results obtained in 17 of such patients were described.

Very high levels were obtained in a giant aged 13 years while in two patients with hypopituitary dwarfism and two with presumed hypopituitary hypothyroidism growth hormone was practically absent from the serum.

GRANVILLE NICKERSON (Montreal). 'Electroencephalographic Observations on Fifty Children Recovered from Tuberculous Meningitis.' Electroencephalographic changes have been observed in a group of 50 children who have recovered from tuberculous meningitis. These electroencephalograms are discussed from the point of view of: (1) Their specific diagnostic value in tuberculous meningitis; (2) Whether early abnormal changes in the electroencephalogram are indicative of subsequent course of clinical disease; (3) Whether the electroencephalographic pattern is helpful in predicting future intellectual sequelae; (4) In which cases the electroencephalogram may be expected to return to normal, if at all.

These observations have been made over a period of 10 years.

T. OPPÉ, introduced by Professor A. V. Neale (Bristol). 'Foetal and Adult Haemoglobins in Haemolytic Disease of the Newborn.' The distribution of foetal and adult haemoglobin fractions has been measured in 37 infants with rhesus haemolytic disease. The maturity of these infants varied from 35-40 weeks of gestation. It was found that the proportion of adult haemoglobin was increased in affected infants at all gestational ages. This increase was due to an increase in concentration of Hb-A as well as decrease in Hb-F. This change is an effect of decreased red cell survival time and random destruction of vulnerable erythrocytes rather than the hitherto held hypotheses of selective destruction of red cells containing Hb-F, or the preferential regeneration of Hb-A.

GERALD H. HOLMAN (Saskatchewan) and NATHAN GOLUBOFF. 'Familial Non-haemolytic Jaundice with Kernicterus: Studies of Glucuronidation in the Newborn Period in Twins with this Disease.' Children born with an inherited deficiency in their ability to glucuronidate bilirubin, as described by Crigler and Najjar in 1952, always develop severe jaundice with kernicterus and usually die.

Twin male infants aged approximately 13 days were referred to one of the authors (N.G.), because of increasing jaundice developing soon after birth. The first infant died within a few days with severe kernicterus and the second died 10 months later. Studies of the ability of these infants to glucuronidate intravenously infused radioactive and non-radioactive adrenal steroids

supports the opinion that these children have a marked deficiency in liver glucuronidation. Attempts to delineate heterozygotes in the family tree will be presented.

G. H. VALENTINE (London, Canada). 'Heparinized Blood Exchange Transfusion and a Slow Continuous Drip Method.' Personal experience of 95 exchange transfusions with heparinized blood will be described. A small successful trial of hexadimethrine bromide (polybrene) as a heparin antagonist was made.

During the past year a slow continuous drip method of exchange transfusion has been used where hyperbilirubinaemia is the main concern. No elaborate equipment is required. More bilirubin can be cleared from the body than by the usual method. Donation and removal of blood are self-regulating, and the exchange transfusion can be supervised by a nurse.

ALLISON D. McDONALD, introduced by Professor Paul E. Polani (London). 'Neurological Disorders in Children of Very Low Birth Weight.' 1,127 infants weighing 4 lb. or less at birth were included in an M.R.C. study of retrolental fibroplasia in 1951-53. In collaboration with the Society of Medical Officers of Health the children were traced in 1959-60 through school health services and a report from a health visitor obtained in all but 20. Specialist opinions were sought on children with neurological abnormalities; those with delayed motor development and many with cerebral palsy were personally visited. Cerebral palsy was found in 6% and mental defect in another 2%. In addition, 7% of children had a history of convulsions, 1% perceptive deafness and 1% other neurological abnormalities.

PIERRE H. BEAUDRY (Montreal), DR. L. D. PENGELLY and DR. D. V. BATES. 'Reappraisal of Ability to Maintain Therapeutic Levels of Gas Concentrations and Humidity in Croupettes.' Repeated spot check gas analyses of oxygen concentration in closed top canopies ('Croupettes') are often below 40%. Very little work has been done using continuous monitoring of gas concentration. We have constructed a mobile unit that continuously monitors and records helium and nitrogen concentration, temperature and humidity.

Analysis of results to date are as follows: (a) The level of oxygen can be maintained above 40% over a 24-hour period without difficulty. High humidity can also be maintained. (b) Virtually zero concentrations of helium exist at the level of the child's pillow even when 60% He and 40% O<sub>2</sub> mixtures are used.

OLIVER FISHER (Rochester) and M. ROBINOW. 'The Detection of Urinary Mucopolysaccharides as a Test for Gargoylism.' The technique of this test is described as follows: A spot of urine is placed on filter paper and placed in a solution of toluidine blue, distilled water and acetic acid, and subsequently washed twice in acetic acid.

The urines of seven children with typical features of Hunter-Hurler syndrome, or gargoylism, have been tested and show an excess of mucopolysaccharides—

more than the equivalent of 25 mg. % of chondroitin sulphate. Sixty children used as controls, varying from a few weeks of age to 14 years, have been tested in a similar way and show little or no excretion of mucopolysaccharides, i.e. less than 10 mg. % of chondroitin sulphate.

This test is considered to be an easy, rapid and reliable screening method for detecting children suspected of suffering from gargoylism.

RICHARD B. GOLDBLOOM (Montreal). 'Controlled Studies of Tocopherol Deprivation and Requirements in the Nutrition of Healthy Premature Infants.' A study is described, in which healthy premature infants, chosen by alternate selection, have been fed three different artificial formulae which differed only in their tocopherol content. The infants were studied at frequent regular intervals through the first six months of life. Growth and development, haematological changes, serum tocopherol levels and certain phases of erythrocyte enzymatic activity were measured.

From the results of these and earlier studies, it is felt that conclusions can be drawn regarding the biochemical and histological features of the tocopherol deficiency state in man, and the question of tocopherol supplementation in health and disease.

C. C. FORSYTH and D. M. CATHRO, introduced by Professor J. L. Henderson (Dundee). 'A Study of Adrenal Cortical Function in the Newborn Period.'

(a) Dr. C. C. Forsyth: '17-oxosteroids in the Urine of Newborn Infants.' A new method for the separation of urinary steroids by paper chromatography is briefly outlined. The values obtained are corrected according to the recovery of radioactive tracer compounds. The validity of the method is illustrated by comparison of the values obtained for adult males with those of other workers. Results from adult females and mothers are also given.

Full-term and premature infants excrete small quantities of the seven known 17-oxosteroids and also several unknown compounds. The output of these compounds, which may be derived from the foetal cortex, diminishes during the first week of life.

(b) Dr. D. M. Cathro: 'Corticosteroids in the Urine of Newborn Infants.' The metabolism of cortisol in the normal adult, in women at the end of pregnancy, and in the newborn infant is discussed.

Chromatographic studies of urinary steroids obtained from pooled urine are used to illustrate current theories of adrenal steroid metabolism in mothers and newborn infants.

The importance of transplacental transfer of corticoids is considered, and the changing pattern of steroid excretion in the first few days of life is demonstrated by studies made on individual infants. Preliminary results suggest that newborn infants have an adequate supply of 'stress' steroids in the period of adaptation to an extra-uterine existence.

MAURICE D. YOUNG (Vancouver). 'The Familial

Incidence of Congenital Malformation of the Heart.' This paper includes an analysis of about 70 families with more than one instance of a congenital malformation of the heart. Brief allusion is made to the types of malformation in the individual families which are divided into proven cases, lesions strongly suspected clinically, but not proven, and malformations where the exact nature of the lesion is not known. The literature is reviewed briefly and an attempt is made to formulate a possible genetic basis for such malformations.

ALEXANDER RUSSELL (London). 'Selective Thyrotrophic Hormone Deficiency: Three Cases of Primary Hypothalamo-hypophysial Hypothyroidism: Two Familial.' Isolated deficiency of thyrotrophic hormone has not hitherto been defined.

The more specific clinical criteria of hypothyroidism were relatively subtle, and I.Q. levels were consistently normal. Moreover, serum cholesterol was normal in the brothers. Nevertheless, the P.B.I. was unequivocally low (1.6%), although  $I^{131}$  uptake showed borderline subnormality. Striking elevation of these indices (and of growth)—and almost euthyroid status—followed stimulation with T.S.H. indicating endogenous deficiency thereof.

No other pituitary dysfunction was revealed, and normal growth and gonadotrophic function were confirmed by progress on thyroxine. Hypothalamic integrations regulate thyrotrophic secretion, so that either hypothalamic or pituitary levels are primarily affected.

W. A. COCHRANE (Halifax, Nova Scotia). 'Vitamin D Resistant Rickets.' Twelve cases of non-nutritional rickets are described; 11 cases were recognized as hypophosphataemic vitamin D resistant rickets: one with cystinosis, six with simple hypophosphataemic rickets, one with Lowe's syndrome (oculo-cerebral-renal syndrome), two with hypophosphataemia, glycosuria, acidosis and aminoaciduria, and one with hypophosphataemia, glycosuria and acidosis. One patient had hypoplastic kidneys, marked bone changes, acidosis and growth failure.

Investigation has included the effect of calcium infusion on urinary phosphate reabsorption, and percutaneous renal biopsy in eight cases. Calcium infusion studies suggest that parathyroid function is decreased and support the hypothesis that the hyperphosphaturia and hypophosphataemia may be due to secondary hyperparathyroidism because of defective absorption of calcium or defective vitamin D metabolism resulting in defective calcium absorption.

JOHN LORBER (Sheffield). 'Hereditary Factors in Meningomyelocele.' The family trees of several hundred babies born with meningomyelocele have been studied and the incidence of similar or allied malformations in the C.N.S. was found to be very high, suggesting that this condition is due to a recessive gene.

LAWRENCE LAWN, introduced by Professor R. A. McCance. 'Demonstration of an Artificial Placenta.'

The apparatus consists of an oxygenator, a dialyser and a container for the foetus. After catheterization of the umbilical vessels, blood, which has passed through the oxygenator and then through the dialyser, is offered to the foetal vein at a low and variable pressure. The blood returns through the umbilical arteries to the oxygenator at a higher, but also variable, pressure, thus maintaining the circulation.

Drop counters record the blood flow to and from the foetus and an E.C.G. records the cardiac rhythm.

The foetus lies in an enclosed vessel in isotonic glucose solution. Hence the amniotic pressure can also be varied.

#### Symposium on the Respiratory Distress Syndrome in the Newborn Infant

##### Opening Speakers:

JOHN DAVIS: 'Experimentally Induced Respiratory Distress in Newborn Rabbits.' If baby rabbits are delivered near term by caesarian section, they can survive up to 20 minutes' birth anoxia or asphyxia. Depending on the mode of induction, this is followed either by rapid recovery on resuscitation or by prolonged respiratory distress. Experimental results are reported which suggest that expansion of the lungs with isotonic fluid rather than with gas at birth results in the subsequent development of acute pulmonary oedema and that such a situation can occur when a foetus is partially asphyxiated *in utero* and allowed to recover before delivery. This may have a bearing on the pathogenesis of respiratory distress in the human premature infant.

LEONARD STRANG: 'Ventilatory Failure in Infants with Respiratory Distress.' Newborn infants with severe respiratory distress were investigated by analysis of arterial blood gases during the breathing of pure  $O_2$ . In addition, expired gas was analysed at the nostril using a mass spectrometer. Babies with respiratory distress have an abnormally low level of alveolar ventilation and they may also develop right to left cardiovascular shunting. Possible mechanisms connecting these events are discussed.

R. E. BONHAM CARTER: 'Observations of Flow through the Ductus Arteriosus in Premature Babies.' Four ways in which the ductus arteriosus has been observed to behave in premature babies are recorded. These are: closing within 36 hours with no further recurrence or disability; remaining patent and causing congestive cardiac failure requiring ligation; remaining patent almost to the expected date of delivery and then closing with minor disability only, and apparently opening and closing with the occurrence of episodes of respiratory distress.

K. W. CROSS: 'Pulmonary Inflation in the Newborn.' Two aspects of pulmonary inflation will be considered. The pulmonary vascular consequences of inflation of the unexpanded lungs, as described by Dawes and his colleagues will be discussed first. Essentially they have found that positive pressure inflation of the lung with a

leads to a diminution in pulmonary vascular resistance, and a great increase in pulmonary blood flow. Secondly, the consequences of pulmonary inflation in the newborn human will be discussed. It has been found that lung inflation in the very young baby leads to a gasp, which obviously accentuates the effect of any applied pressure. The response is different from that found in the adult. The possible inferences of this will be the subject for further speculation.

The afternoon of Thursday, June 28, was spent in

social activities with tours of the Colleges, punting on the river, visits to the Botanic Gardens and the Fitzwilliam Museum. By courtesy of Messrs. Cow and Gate, trips to Ely Cathedral and Sawston Hall were arranged.

The Ulster Cup Golf competition was held and was won by Dr. B. McNicholl.

The Annual Dinner was held in the Guildhall on the evening of Thursday, June 29. The James Spence Medal for 1960 was presented to Professor A. A. Moncrieff and the James Spence Medal for 1961 was presented to Professor R. A. McCance.

## BOOK REVIEWS

**Fetal Electrocardiography: The Electrical Activity of the Fetal Heart.** By SAUL DAVID LARKS. (Pp. xiii + 109; 70 figures. 52s.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1961.

At last the world has its first textbook on Foetal (Fetal) Electrocardiography; it is well and authoritatively written by a biophysicist with considerable personal experience of the subject. It is over 30 years since Sherrington declared the 'one-man text-book' dead, but were it necessary to wait for a co-operative effort from the 240 authors who have entered the lists since 1906 then the subject would remain in relative obscurity, and thousands of foetal lives would continue to be lost unnecessarily every year.

Every medical man concerned with foetal welfare, or the care of the newborn, and not already experienced in the application of foetal electrocardiography should read this book and follow its references.

The supposition that the electrocardiogram of the newborn, and hence of the foetus, is not properly established and suitable for diagnostic purposes, if still held, must be discarded. The examples in this book alone are sufficient to show that from 16, if not 11, weeks of gestation the wave patterns resemble the adult forms in both normal and abnormal conditions.

The foetal electrocardiogram provides the obstetrician with the diagnosis of pregnancy and multiple pregnancy from 11 weeks gestation, it reveals certain types of congenital heart disease and it guides the treatment of threatened abortion.

The contribution which the foetal electrocardiogram can make to a reduction in perinatal mortality is revealed in the latter part of pregnancy and during labour and delivery. Frequent electrocardiograms are necessary for foetal health can suffer abrupt changes. Bradycardia must not be allowed to persist and silent extrasystoles are a sign of early reversible metabolic deficiencies. The changes in pattern during uterine contractions or with medical induction of labour or with surgical manoeuvres prepare the paediatrician to accept a baby with respiratory disorders or metabolic acidosis. The instrument helps the obstetrician to conduct labour on a rational basis, to intervene when necessary and to appreciate quickly the effectiveness of conservative measures to relieve foetal distress.

The introduction of this book will set a problem for the reader, because he will feel the need for £500 worth of apparatus and for a service of technicians 24 hours a day and every day. The recordings are required frequently in pregnancy and quarter-hourly, if not continuously, in labour. The reviewer's estimate of the costs of this work is £2 per patient and £200 per baby's life saved (assuming a reduction in perinatal mortality to  $2\frac{1}{2}$  from  $3\frac{1}{2}\%$ ). So far the National Health Service have not accepted the financial challenge but, as experience grows, shoulders must be found to bear the decision of saving or not saving lives through the use of this instrument. If the author of this textbook accelerates this decision then he will render a substantial service to medicine.

The reviewer would not fulfil his task if he did not regret the haste with which the text has been corrected, e.g. the rare use of the word 'metal' for 'foetal' and an anagram for 'maintenance', and the Gaussian distribution of commas. The first chapters could preface any book on electrophysiology and, indeed, parts of them, including the spirit photograph of Einthoven and his vector shadows across the quartered heart are common to 'Electrohysterography' by the same author and publishers. Of the 44 references, 25% are to the author's own work. It is a pity that the published work (Hildebrand, 1960; Reygaerts, 1958, 1959; Smyth and Farrow, 1958; Smyth, 1960) on the persistence of the foetal electrocardiogram in certain cases of severe peripheral maceration is not included; nor is the work (Bieniarz and Reynolds, 1960) on the effects of maternal venous pressure on foetal heart rate given sufficient importance.

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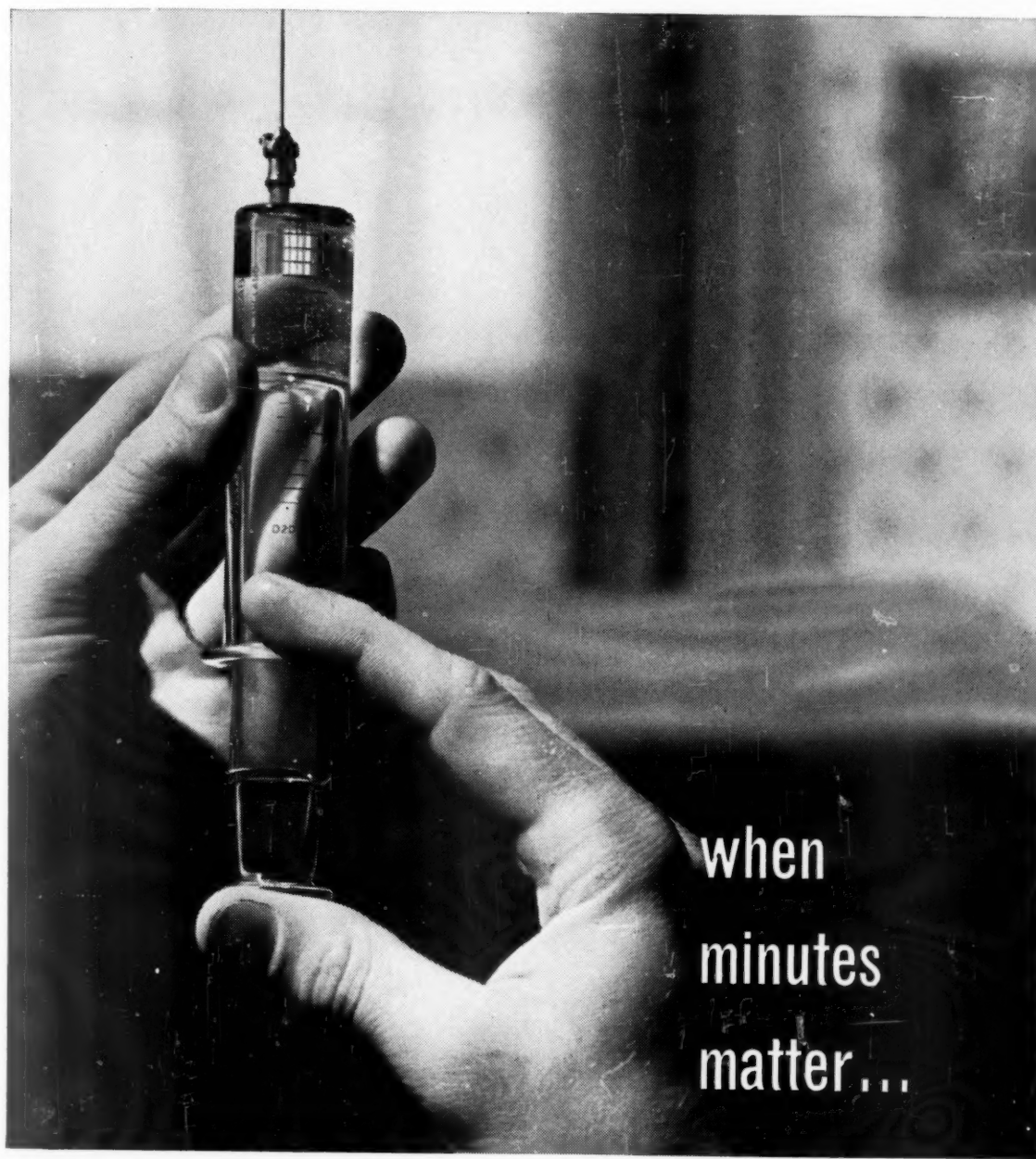
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